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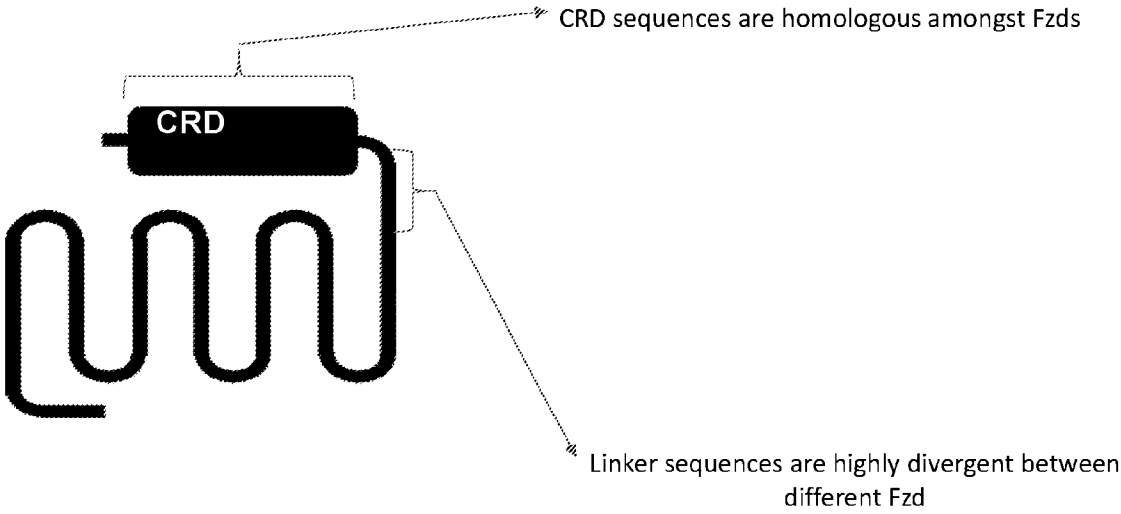

FIG. 1

(57) Abrégé/Abstract:
The present invention provides anti-Fzd monoclonal antibodies and related compositions, which may be used in any of a variety of therapeutic methods for the treatment of diseases.

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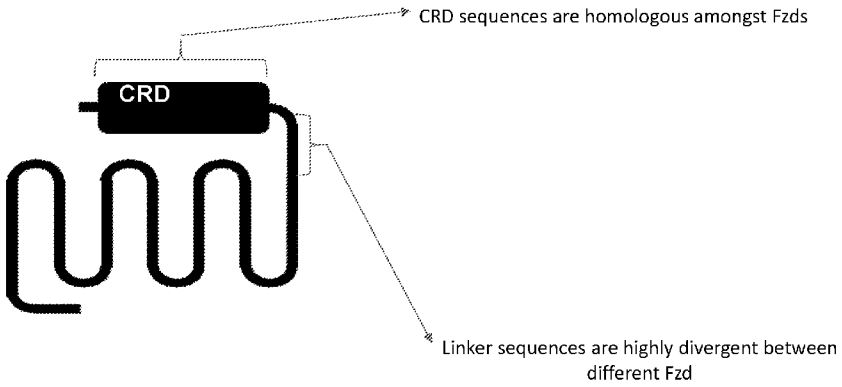

FIG. 1

(57) Abstract: The present invention provides anti-Fzd monoclonal antibodies and related compositions, which may be used in any of a variety of therapeutic methods for the treatment of diseases.

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MONOSPECIFIC ANTI-FRIZZLED ANTIBODIES AND METHODS OF USE

Cross Reference to Related Applications

This application claims priority to U.S. Provisional Application No. 62/869,976, filed July 2, 2019, and U.S. Provisional Application No. 62/875,073, filed July 17, 2019, each of which is incorporated by reference herein in its entirety.

Statement Regarding Sequence Listing

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is SRZN_017_02WO_ST25.txt. The text file is 1.027 MB, created on July 1, 2020, and is being submitted electronically via EFS-Web.

BACKGROUND

Technical Field

The present invention relates generally to monospecific anti-Frizzled antibodies and antigen-binding fragments thereof, compositions, and methods of using the same. Such antibodies are useful, for example, in modulating Wnt signaling pathways.

Description of the Related Art

Wnt ("Wingless-related integration site" or "Wingless and Int-1" or "Wingless-Int") ligands and their signals play key roles in the control of development, homeostasis and regeneration of many essential organs and tissues, including bone, liver, skin, stomach, intestine, kidney, central nervous system, mammary gland, taste bud, ovary, cochlea and many other tissues (reviewed, e.g., by Clevers, Loh, and Nusse, 2014; 346:1248012). Modulation of Wnt signaling pathways has potential for treatment of degenerative diseases and tissue injuries.

One of the challenges for modulating Wnt signaling as a therapeutic is the existence of multiple Wnt ligands and Wnt receptors, Frizzled 1-10 (Fzd1-10), with many tissues expressing multiple and overlapping Fzds. Canonical Wnt signals also

involve Low-density lipoprotein (LDL) receptor-related protein 5 (LRP5) or Low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) as co-receptors, which are broadly expressed in various tissues, in addition to Fzds. Accordingly, there is clearly a need in the art for binding moieties, such as antibodies, that specifically bind to one or more Fzd, LRP5, or LRP6. The present invention addresses this need.

BRIEF SUMMARY

In various embodiments, the present invention provides anti-Fzd antibodies and antigen-binding fragments thereof and related methods of use.

In one embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds to one or more Frizzled receptor, comprising a sequence comprising: (i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 1; and/or (ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 1, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, are humanized. In certain embodiments, any of the antibodies, or antigen-binding fragments thereof, are a single chain antibody, a scFv, a univalent antibody lacking a hinge region, a VHH or single domain antibody (sdAb), or a minibody. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, are a Fab or a Fab' fragment.

In certain embodiments, any of the antibodies, or antigen-binding fragments thereof, are a fusion protein. In certain embodiments, the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds LRP5 or LRP6. In certain embodiments, the polypeptide sequence that binds LRP5 or LRP6 is an antibody, or an antigen-binding fragment thereof, that binds to LRP5 or LRP6.

In particular embodiments of any of the antibodies, or antigen-binding fragments thereof, the antibody, or antigen-binding fragment thereof, binds to Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

In a related embodiment, the disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that competes with any of the antibodies disclosed herein for binding to a human Fzd receptor.

In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, bind to the Fzd with a KD of 50 μM or lower.

In particular embodiments, any of the antibodies, or antigen-binding fragments thereof, modulate a Wnt signaling pathway in a cell, optionally a mammalian cell. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof increase signaling via a Wnt signaling pathway in the cell. In particular embodiments, any of the antibodies, or antigen-binding fragments thereof decrease signaling via a Wnt signaling pathway in the cell. In certain embodiments, the Wnt signaling pathway is a canonical Wnt signaling pathway or a non-canonical Wnt signaling pathway.

In a further related embodiment, the present disclosure provides an isolated polynucleotide encoding an antibody, or antigen-binding fragment thereof, disclosed herein. In certain embodiments, the present disclosure provides an expression vector comprising the isolated polynucleotide and an isolated host cell comprising the expression vector.

In another embodiment, the present disclosure provides a pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, disclosed herein.

In a further embodiment, the present disclosure provides a method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell with an isolated antibody, or antigen-binding fragment thereof, disclosed herein that increases Wnt signaling. In particular embodiments, the antibody, or antigen-binding fragment thereof, is a fusion protein comprising a polypeptide sequence that binds LRP5 or LRP6.

In another embodiment, the present disclosure provides a method for inhibiting a Wnt signaling pathway in a cell, comprising contacting the cell with the isolated antibody, or antigen-binding fragment thereof, disclosed herein the inhibits Wnt signaling.

In another embodiment, the present disclosure includes a method for treating a subject having a disease or disorder associated with reduced Wnt signaling, comprising administering to the subject an effective amount of a pharmaceutical composition comprising an isolated antibody, or antigen-binding fragment thereof, disclosed herein that is an agonist of a Wnt signaling pathway. In particular embodiments, the disease or disorder is selected from the group consisting of: bone fractures, stress fractures, vertebral compression fractures, osteoporosis, osteoporotic fractures, non-union fractures, delayed union fractures, spinal fusion, pre-operative optimization for spine surgeries, osteonecrosis, osseointegration of implants or orthopedic devices, osteogenesis imperfecta, bone grafts, tendon repair, tendon-bone integration, tooth growth and regeneration, maxillofacial surgery, dental implantation, periodontal diseases, maxillofacial reconstruction, osteonecrosis of the jaw, hip or femoral head, avascular necrosis, alopecia, hearing loss, vestibular hypofunction, macular degeneration, age-related macular degeneration (AMD), vitreoretinopathy, retinopathy, diabetic retinopathy, diseases of retinal degeneration, Fuchs' dystrophy, cornea diseases, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, diseases affecting blood brain barrier (BBB), spinal cord injuries, spinal cord diseases, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), Crohn's disease (CD), ulcerative colitis (UC), in particular CD with fistula formation, metabolic syndrome, dyslipidemia, diabetes, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, pressure sores, venous leg ulcers, epidermolysis bullosa, dermal hypoplasia, myocardial infarction, coronary artery disease, heart failure, hematopoietic cell disorders, immunodeficiencies, graft versus host diseases, acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, end stage liver disease (ESLD), nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, livery surgery, liver injury, liver transplantation, "small for size" syndrome in liver surgery and

transplantation, congenital liver disease and disorders, any other liver disorder or detect resulting from genetic diseases, degeneration, aging, drugs, or injuries.

In a related embodiment, the present disclosure provides a method for treating a subject having a disease or disorder associated with increased or enhanced Wnt signaling, comprising administering to the subject an effective amount of the pharmaceutical composition comprising an isolated antibody, or antigen-binding fragment thereof, disclosed herein that is an inhibitor of a Wnt signaling pathway. In certain embodiments, the disease or disorder is selected from the group consisting of: tumors and cancers, degenerative disorders, fibrosis, heart failure, coronary artery disease, heterotopic ossification, osteopetrosis, and congenital high bone mass disorders.

In a further related embodiment, the present disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds one or an epitope within a region of Frizzled 8 comprising or consisting of amino acid residues 55-137.

In certain embodiments, the present disclosure provides an isolated antibody, or an antigen-binding fragment thereof, that binds one or more Frizzled receptor, wherein the antibody or antigen-binding fragment thereof contacts the Frizzled receptor with a distance of less than 5 angstroms, or between 5 and 8 angstroms at any of the sets of amino acid residues indicated in Table 4.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. Schematic diagram of a Fzd receptor including a cysteine rich domain (CRD), hinge region, and N-terminal region.

FIG. 2. Illustration of the Wnt surrogate molecule structure. White ovals represent sdAb or VHH binding molecules specific for LRP5, LRP6 or LRP; gray ovals are the monospecific Fzd Fab binding molecules; and the black ovals are IgG CH2 and CH3 domains. The sdAb or VHH binding molecules are attached to the N-termini of the light chains, with or without a linker.

FIG. 3. Percent identity and sequence comparison of Fzd1 (SEQ ID NO: 1), Fzd2 (SEQ ID NO: 2) and Fzd7 (SEQ ID NO: 7) hinge regions.

FIGS. 4A-H. Binding kinetics of 33SB3 (FIGS. 4A and 4B), 33SD2 (FIGS. 4C and 4D), 33SE2 (FIGS. 4E and 4F) and 31SB2 (FIGS. 4G and 4H) Fabs.

FIGS. 5A-B. In vitro activity of 33SB3-36, 33SD2-3, 33SE2-36 (FIG. 5A), and 31SB2-36 (FIG. 5B) Wnt surrogate molecules.

FIGS. 6A-6B. Shows the binding residues of crystallized 027S-E05:hFzd8. Fig. 6A depicts the overall structure of Fzd8:27SE5 complex. Molecular-surface of Fzd8 shown in light-gray transparent surface. Heavy- and Light- chains of 27SE5 are colored in shades of darker- and lighter- black, respectively. The lipid (palmitoleic acid; PAM) as observed in the structure of Wnt8:Fzd8 (PDB code: 4F0A) is shown in light-gray spheres. Fig. 6B is a close-up view of the Fzd8:27SE5 interface with positions of CDR loops H1, H2, H3 of heavy-chain and L1, L2, and L3 of light-chain are marked. Glycosylation on Fzd8 is shown in sticks representation.

DETAILED DESCRIPTION

The present disclosure relates to antibodies and antigen-binding fragments thereof that specifically a Fzd receptor, including antibodies having particular Fzd receptor specificity and/or functional properties. One embodiment of the invention encompasses specific humanized antibodies and fragments thereof capable of binding to a Fzd receptor and modulate downstream Wnt pathway signaling and related biological effects.

Embodiments of the invention pertain to the use of anti-Fzd antibodies or antigen-binding fragments thereof for the diagnosis, assessment and treatment of diseases and disorders associated with Wnt signaling pathways. In certain embodiments, the subject antibodies and antigen-binding fragments thereof are used to modulate a Wnt signaling pathway in a cell or tissue. In certain embodiments, the subject antibodies and antigen-binding fragments thereof are used in the treatment or prevention of diseases and disorders associated with aberrant or deregulated (e.g., either increased or reduced) Wnt signaling, or for which either decreasing or increasing Wnt signaling would provide a therapeutic benefit.

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, *Current Protocols in Molecular Biology* or *Current Protocols in Immunology*, John Wiley & Sons, New York, N.Y.(2009); Ausubel *et al.*, *Short Protocols in Molecular Biology*, 3rd ed., Wiley & Sons, 1995;

Sambrook and Russell, *Molecular Cloning: A Laboratory Manual* (3rd Edition, 2001); Maniatis *et al. Molecular Cloning: A Laboratory Manual* (1982); *DNA Cloning: A Practical Approach*, vol. I & II (D. Glover, ed.); *Oligonucleotide Synthesis* (N. Gait, ed., 1984); *Nucleic Acid Hybridization* (B. Hames & S. Higgins, eds., 1985); *Transcription and Translation* (B. Hames & S. Higgins, eds., 1984); *Animal Cell Culture* (R. Freshney, ed., 1986); Perbal, *A Practical Guide to Molecular Cloning* (1984) and other like references.

As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the content clearly dictates otherwise.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Each embodiment in this specification is to be applied *mutatis mutandis* to every other embodiment unless expressly stated otherwise.

Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. These and related techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of, molecular biology, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques may be used for recombinant technology, molecular biological, microbiological, chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of subjects.

Embodiments of the present invention relate to antibodies and antigen-binding fragments thereof that bind to one or more Fzd receptor. Sequences of illustrative

antibodies, or antigen-binding fragments, or complementarity determining regions (CDRs) thereof, are set forth in Table 1.

As is well known in the art, an antibody is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one epitope recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as dAb, Fab, Fab', $F(ab')_2$, Fv), single chain (scFv), VHH or sdAb (also known as a Nanobody®), synthetic variants thereof, naturally occurring variants, fusion proteins comprising an antibody or an antigen-binding fragment thereof, humanized antibodies, chimeric antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding site or fragment (epitope recognition site) of the required specificity. "Diabodies", multivalent or multispecific fragments constructed by gene fusion (WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993) are also a particular form of antibody contemplated herein. Minibodies comprising a scFv joined to a CH3 domain are also included herein (S. Hu et al., Cancer Res., 56, 3055-3061, 1996). See *e.g.*, Ward, E. S. *et al.*, Nature 341, 544-546 (1989); Bird et al., Science, 242, 423-426, 1988; Huston et al., PNAS USA, 85, 5879-5883, 1988); PCT/US92/09965; WO94/13804; P. Holliger et al., Proc. Natl. Acad. Sci. USA 90 6444-6448, 1993; Y. Reiter et al., Nature Biotech, 14, 1239-1245, 1996; S. Hu et al., Cancer Res., 56, 3055-3061, 1996.

The term "antigen-binding fragment" as used herein refers to a polypeptide fragment that contains at least one CDR of an immunoglobulin heavy and/or light chain that binds to the antigen of interest, in particular to one or more Fzd receptor. In this regard, an antigen-binding fragment of the herein described antibodies may comprise 1, 2, 3, 4, 5, or all 6 CDRs of a VH and VL sequence set forth herein from antibodies that bind one or more Fzd receptor. An antigen-binding fragment of the Fzd-specific antibodies described herein is capable of binding to a Fzd receptor. As used herein, the term encompasses not only isolated fragments but also polypeptides comprising an antigen-binding fragment of an antibody disclosed

herein, such as, for example, fusion proteins comprising an antigen-binding fragment of an antibody disclosed herein.

In certain embodiments, an antibody or antigen-binding fragment thereof, modulates Wnt signaling events in a cell contacted with the antibody or antigen-binding fragment thereof. In certain embodiments, the antibody or antigen-binding fragment thereof increases Wnt signaling, while in other embodiments, it decreases Wnt signaling. In certain embodiments, the antibody or antigen-binding fragment thereof binds specifically to and/or modulates the biological activity of the human Wnt signaling pathway.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. In certain embodiments, an antibody is said to specifically bind an antigen when it preferentially recognizes its target antigen in a complex mixture of proteins and/or macromolecules. In certain embodiments, an antibody is said to specifically bind an antigen when the equilibrium dissociation constant is $\leq 10^{-7}$ or 10^{-8} M. In some embodiments, the equilibrium dissociation constant may be $\leq 10^{-9}$ M or $\leq 10^{-10}$ M.

In certain embodiments, antibodies and antigen-binding fragments thereof as described herein include a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain framework region (FR) set which provide support to the CDRs and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the

heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRs. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures—regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

The structures and locations of immunoglobulin CDRs and variable domains may be determined by reference to Kabat, E. A. et al., Sequences of Proteins of Immunological Interest. 4th Edition. US Department of Health and Human Services. 1987, and updates thereof, now available on the Internet (immuno.bme.nwu.edu). Alternatively, CDRs may be determined by using "IMGT®, the international ImMunoGeneTics information system® available at http://www.imgt.org (see, e.g., Lefranc, M.-P. et al. (1999) *Nucleic Acids Res.*, 27:209-212; Ruiz, M. et al. (2000) *Nucleic Acids Res.*, 28:219-221; Lefranc, M.-P. (2001) *Nucleic Acids Res.*, 29:207-209; Lefranc, M.-P. (2003) *Nucleic Acids Res.*, 31:307-310; Lefranc, M.-P. et al. (2004) *In Silico* Biol., 5, 0006 [Epub], 5:45-60 (2005)]; Lefranc, M.-P. et al. (2005) *Nucleic Acids Res.*, 33:D593-597; Lefranc, M.-P. et al. (2009) *Nucleic Acids Res.*, 37:D1006-1012; Lefranc, M.-P. et al. (2015) *Nucleic Acids Res.*, 43:D413-422). The CDRs of the antibodies described herein were determined using either the IMGT® system or using the Abgenesis software from Distributed Bio to map the specificity determining regions (SDRs) shown below, which include the Kabat definition of CDRs (Padlan et al. *FASEB J.* 9, 133-139 (1995).

A “monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an epitope. Monoclonal antibodies are highly specific, being directed against a single epitope. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$, Fv), single chain (scFv), VHH or sdAb, variants thereof, fusion proteins comprising an antigen-binding fragment of a monoclonal antibody, humanized monoclonal antibodies, chimeric monoclonal antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen-binding fragment (epitope recognition site) of the required specificity and the ability to bind to an epitope. It is not intended to be limited as regards the source of the antibody or the manner in which it is made (*e.g.*, by hybridoma, phage selection, recombinant expression, transgenic animals, etc.). The term includes whole immunoglobulins as well as the fragments etc. described above under the definition of "antibody".

The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the F(ab) fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the $F(ab')_2$ fragment which comprises both antigen-binding sites. An Fv fragment for use according to certain embodiments of the present invention can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions of an IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent $V_H::V_L$ heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar *et al.* (1972) *Proc. Nat. Acad. Sci. USA 69*:2659-2662; Hochman *et al.* (1976) *Biochem 15*:2706-2710; and Ehrlich *et al.* (1980) *Biochem 19*:4091-4096.

In certain embodiments, single chain Fv or scFV antibodies are contemplated. For example, Kappa bodies (Ill *et al.*, *Prot. Eng*. 10: 949-57 (1997); minibodies (Martin *et al.*, *EMBO J* 13: 5305-9 (1994); diabodies (Holliger *et al.*, *PNAS* 90: 6444-8 (1993); or Janusins (Traunecker *et al.*, *EMBO J* 10: 3655-59 (1991) and

Traunecker *et al., Int. J. Cancer Suppl.* 7: 51-52 (1992), may be prepared using standard molecular biology techniques following the teachings of the present application with regard to selecting antibodies having the desired specificity. In still other embodiments, bispecific or chimeric antibodies may be made that encompass the ligands of the present disclosure. For example, a chimeric antibody may comprise CDRs and framework regions from different antibodies, while bispecific antibodies may be generated that bind specifically to one or more Fzd receptor through one binding domain and to a second molecule through a second binding domain. These antibodies may be produced through recombinant molecular biological techniques or may be physically conjugated together.

A single chain Fv (scFv) polypeptide is a covalently linked V_H::V_L heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston *et al.* (1988) *Proc. Nat. Acad. Sci. USA 85*(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated—but chemically separated—light and heavy polypeptide chains from an antibody V region into an scFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston *et al.*; and U.S. Pat. No. 4,946,778, to Ladner *et al.*

In certain embodiments, a Fzd binding antibody as described herein is in the form of a diabody. Diabodies are multimers of polypeptides, each polypeptide comprising a first domain comprising a binding region of an immunoglobulin light chain and a second domain comprising a binding region of an immunoglobulin heavy chain, the two domains being linked (*e.g.* by a peptide linker) but unable to associate with each other to form an antigen binding site: antigen binding sites are formed by the association of the first domain of one polypeptide within the multimer with the second domain of another polypeptide within the multimer (WO94/13804).

A dAb fragment of an antibody consists of a VH domain (Ward, E. S. *et al.*, Nature 341, 544-546 (1989)).

Where bispecific antibodies are to be used, these may be conventional bispecific antibodies, which can be manufactured in a variety of ways (Holliger, P. and Winter G. *Current Opinion Biotechnol.* 4, 446-449 (1993)), *e.g.* prepared

chemically or from hybrid hybridomas, or may be any of the bispecific antibody fragments mentioned above. Diabodies and scFv can be constructed without an Fc region, using only variable domains, potentially reducing the effects of anti-idiotypic reaction.

Bispecific diabodies, as opposed to bispecific whole antibodies, may also be particularly useful because they can be readily constructed and expressed in *E. coli*. Diabodies (and many other polypeptides such as antibody fragments) of appropriate binding specificities can be readily selected using phage display (WO94/13804) from libraries. If one arm of the diabody is to be kept constant, for instance, with a specificity directed against antigen X, then a library can be made where the other arm is varied and an antibody of appropriate specificity selected. Bispecific whole antibodies may be made by knobs-into-holes engineering (J. B. B. Ridgeway et al., *Protein Eng.*, 9, 616-621, 1996).

In certain embodiments, the antibodies described herein may be provided in the form of a UniBody®. A UniBody® is an IgG4 antibody with the hinge region removed (see GenMab Utrecht, The Netherlands; see also, *e.g.*, US20090226421). This proprietary antibody technology creates a stable, smaller antibody format with an anticipated longer therapeutic window than current small antibody formats. IgG4 antibodies are considered inert and thus do not interact with the immune system. Fully human IgG4 antibodies may be modified by eliminating the hinge region of the antibody to obtain half-molecule fragments having distinct stability properties relative to the corresponding intact IgG4 (GenMab, Utrecht). Halving the IgG4 molecule leaves only one area on the UniBody® that can bind to cognate antigens (*e.g.*, disease targets) and the UniBody® therefore binds univalently to only one site on target cells.

In certain embodiments, the antibodies of the present disclosure may take the form of a VHH or sdAb. VHH or sdAb technology was originally developed following the discovery and identification that *camelidae* (e.g., camels and llamas) possess fully functional antibodies that consist of heavy chains only and therefore lack light chains. These heavy-chain only antibodies contain a single variable domain(V_{HH}) and two constant domains (C_H2, C_H3). The cloned and isolated single variable domains have full antigen binding capacity and are very stable. These single variable

domains, with their unique structural and functional properties, form the basis of "VHH or sdAb". VHH or sdAb are encoded by single genes and are efficiently produced in almost all prokaryotic and eukaryotic hosts *e.g. E. coli* (see *e.g.* U.S. Pat. No. 6,765,087), molds (for example *Aspergillus* or *Trichoderma*) and yeast (for example *Saccharomyces, Kluyvermyces, Hansenula* or *Pichia* (see *e.g.* U.S. Pat. No. 6,838,254). The production process is scalable and multi-kilogram quantities of VHH or sdAb have been produced. VHH or sdAb may be formulated as a ready-to-use solution having a long shelf life. The Nanoclone® method (see, e.g., WO 06/079372) is a proprietary method for generating VHH or sdAb against a desired target, based on automated high-throughput selection of B-cells. VHH or sdAb are single-domain antigen-binding fragments of camelid-specific heavy-chain only antibodies. VHH or sdAb, typically have a small size of around 15 kDa.

In certain embodiments, the anti-Fzd antibodies or antigen-binding fragments thereof as disclosed herein are humanized. This refers to a chimeric molecule, generally prepared using recombinant techniques, having an antigen-binding site derived from an immunoglobulin from a non-human species and the remaining immunoglobulin structure of the molecule based upon the structure and/or sequence of a human immunoglobulin. The antigen-binding site may comprise either complete variable domains fused onto constant domains or only the CDRs grafted onto appropriate framework regions in the variable domains. Epitope binding sites may be wild type or modified by one or more amino acid substitutions. This eliminates the constant region as an immunogen in human individuals, but the possibility of an immune response to the foreign variable region remains (LoBuglio, A. F. *et al.*, (1989) *Proc Natl Acad Sci USA* 86:4220-4224; Queen *et al.*, *PNAS* (1988) 86:10029-10033; Riechmann *et al.*, *Nature* (1988) 332:323-327). Illustrative methods for humanization of the anti-Fzd antibodies disclosed herein include the methods described in U.S. patent no. 7,462,697.

Another approach focuses not only on providing human-derived constant regions, but modifying the variable regions as well so as to reshape them as closely as possible to human form. It is known that the variable regions of both heavy and light chains contain three complementarity-determining regions (CDRs) which vary in response to the epitopes in question and determine binding capability, flanked by

four framework regions (FRs) which are relatively conserved in a given species and which putatively provide a scaffolding for the CDRs. When nonhuman antibodies are prepared with respect to a particular epitope, the variable regions can be "reshaped" or "humanized" by grafting CDRs derived from nonhuman antibody on the FRs present in the human antibody to be modified. Application of this approach to various antibodies has been reported by Sato, K., *et al.*, (1993) *Cancer Res* 53:851-856. Riechmann, L., *et al.*, (1988) *Nature* 332:323-327; Verhoeyen, M., *et al.*, (1988) *Science* 239:1534-1536; Kettleborough, C. A., *et al.*, (1991) *Protein Engineering* 4:773-3783; Maeda, H., *et al.*, (1991) *Human Antibodies Hybridoma* 2:124-134; Gorman, S. D., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:4181-4185; Tempest, P. R., *et al.*, (1991) *Bio/Technology* 9:266-271; Co, M. S., *et al.*, (1991) *Proc Natl Acad Sci USA* 88:2869-2873; Carter, P., *et al.*, (1992) *Proc Natl Acad Sci USA* 89:4285-4289; and Co, M. S. *et al.*, (1992) *J Immunol* 148:1149-1154. In some embodiments, humanized antibodies preserve all CDR sequences (for example, a humanized mouse antibody which contains all six CDRs from the mouse antibodies). In other embodiments, humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

In certain embodiments, the antibodies of the present disclosure may be chimeric antibodies. In this regard, a chimeric antibody is comprised of an antigen-binding fragment of an anti-Fzd antibody operably linked or otherwise fused to a heterologous Fc portion of a different antibody. In certain embodiments, the heterologous Fc domain is of human origin. In other embodiments, the heterologous Fc domain may be from a different Ig class from the parent antibody, including IgA (including subclasses IgA1 and IgA2), IgD, IgE, IgG (including subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. In further embodiments, the heterologous Fc domain may be comprised of CH2 and CH3 domains from one or more of the different Ig classes. As noted above with regard to humanized antibodies, the anti-Fzd antigen-binding fragment of a chimeric antibody may comprise only one or more of the CDRs of the antibodies described herein (*e.g.*, 1, 2, 3, 4, 5, or 6 CDRs of the

antibodies described herein), or may comprise an entire variable domain (VL, VH or both).

In certain embodiments, antibodies or antigen-binding fragments thereof disclosed herein include fusion proteins, e.g., Wnt signaling pathway agonist fusion proteins, also referred to herein as "Wnt surrogates." Wnt surrogates of the present invention are usually biologically active in binding to a cognate Frizzled receptor, and in activation of Wnt signaling, i.e., the surrogate is a Wnt agonist. The term "Wnt agonist activity" refers to the ability of an agonist to mimic the effect or activity of a Wnt protein binding to a frizzled protein. The ability of the agonists of the invention to mimic the activity of Wnt can be confirmed by a number of assays. The agonists of the invention typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the agonists of the invention enhance the canonical Wnt/β-catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of an agonist of the invention.

In particular embodiments, a Wnt signaling pathway agonist fusion protein (or Wnt surrogate) comprises an anti-Fzd antibody, or antigen-binding fragment thereof, disclosed herein fused to a polypeptide that specifically binds to LRP5 and/or LRP6. In particular embodiments, the polypeptide that specifically binds to LRP5 and/or LRP6 is an antibody or antigen-binding fragment thereof. If certain embodiments, it is an antibody or antigen-binding fragment thereof disclosed in application number PCT/US18/66620, titled, "Anti-LRP5/6 antibodies and Methods of Use," Attorney docket number SRZN-005/02WO, filed on December 19, 2018, which is incorporated herein by reference in its entirety.

Suitable LRP5/6 binding domains include, without limitation, de novo designed LRP5/6 binding proteins, antibody derived binding proteins, *e.g.* scFv, Fab, *etc.* and other portions of antibodies that specifically bind to one or more Fzd proteins; VHH or sdAb derived binding domains; knottin-based engineered scaffolds; naturally occurring LRP5/6, including without limitation, DKK1, DKK2, DKK3, DKK4, sclerostin; Wise; fusion proteins comprising any of the above; derivatives of any of the above; variants of any of the above; and biologically active fragments of any of

the above, and the like. A LRP5/6 binding domain may be affinity selected to enhance binding.

Members of the Dickkopf (DKK) gene family (see Krupnik et al. (1999) Gene 238(2):301-13) include DKK-1, DKK-2, DKK-3, and DKK-4, and the DKK-3 related protein Soggy (Sgy). hDKKs 1-4 contain two distinct cysteine-rich domains in which the positions of 10 cysteine residues are highly conserved between family members. Exemplary sequences of human DKK genes and proteins are publicly available, e.g. Genbank accession number NM_014419 (soggy-1); NM_014420 (DKK4); AF177394 (DKK-1); AF177395 (DKK-2); NM_015881 (DKK3); and NM_014421 (DKK2). In some embodiments of the invention, the Lrp6 binding moiety is a DKK1 peptide, including without limitation the C-terminal domain of human DKK1. The C-terminal domain may comprise the sequence: KMYHTKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHG LEIFQRCYCGEGLSCRIQKDHHQASNSSRLHTCQRH (see Genbank accession number NP_036374) (SEQ ID NO:32) or a biologically active fragment thereof.

Binding of DKK proteins to LRP5/6 are discussed, for example in Brott and Sokol Mol. Cell. Biol. 22 (17), 6100-6110 (2002); and Li et al. J. Biol. Chem. 277 (8), 5977-5981 (2002), each herein specifically incorporated by reference. The corresponding region of human DKK2 (Genbank reference NP_055236) may comprise the sequence: KMSHIKGHEGDPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGL EIFQRCDCAKGLSCKVWKDATYSSKARLHVCQK (SEQ ID NO:33) or a biologically active fragment thereof.

Antibodies that specifically bind to LRP5 or LRP6 are known in the art and are commercially available, or can be generated de novo. LRP5, LRP6 or fragments thereof can be used as an immunogen or in screening assays to develop an antibody. Examples of known antibodies include, without limitation, those described in Gong et al. (2010) PLoS One. 5(9):e12682; Ettenberg et al. (2010) Proc Natl Acad Sci U S A. 107(35):15473-8; and those commercially available from, for example Santa Cruz biotechnology antibody clone 1A12, which was raised against synthetic LRP5/6 of human origin and binds to both the full length and proteolytic fragment of

LRP 6 and LRP 5 of mouse and human origin; the monoclonal antibody 2B11; Cell Signaling Technology antibody specific for LRP5 (D80F2), catalog number 5731; etc.

In some embodiments, the LRP5/6 binding domain or element may be selected from any domain that binds LRP5/6 at high affinity, e.g. a K_D of at least about 1 x 10^{-7} M, at least about 1 x 10^{-8} M, at least about 1 x 10^{-9} M, at least about 1 x 10^{-10} M. Suitable LRP5/6 binding domains include, without limitation, de novo designed LRP5/6 binding proteins, antibody derived binding proteins, *e.g.* scFv, Fab, *etc.* and other portions of antibodies that specifically bind to one Fzd protein; VHH or sdAb derived binding domains; knottin-based engineered scaffolds; naturally occurring LRP5/6 binding proteins or polypeptides, including without limitation, Norrin, DKK1, DKK2, DKK3, DKK4, sclerostin; and the like. In certain embodiments the LRP5/6 binding domain is a c-terminal portion of DKK1. A LRP5/6 binding domain may be affinity selected to enhance binding.

The anti-Fzd antibody, or antigen binding fragment thereof, and the LRP5/6 binding domain may be directly joined, or may be separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, etc. The region of the Wnt surrogate that binds one Fzd receptor and the polypeptide that binds LRP5 and/or LRP6 may be contiguous or separated by a linker, e.g. a polypeptide linker, or a non-peptidic linker, *etc.* The length of the linker, and therefore the spacing between the binding domains can be used to modulate the signal strength, and can be selected depending on the desired use of the Wnt surrogate. The enforced distance between binding domains can vary, but in certain embodiments may be less than about 100 angstroms, less than about 90 angstroms, less than about 80 angstroms, less than about 70 angstroms, less than about 60 angstroms, or less than about 50 angstroms. In some embodiments the linker is a rigid linker, in other embodiments the linker is a flexible linker. Where the linker is a peptide linker, it may be from about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 or more amino acids in length, and is of sufficient length and amino acid composition to enforce the distance between binding domains. In some embodiments, the linker comprises or consists of one or more glycine and/or serine residues.

A Wnt surrogate can be multimerized, e.g. through an Fc domain, by concatenation, coiled coils, polypeptide zippers, biotin/avidin or streptavidin multimerization, and the like. The Wnt surrogate can also be joined to a moiety such as PEG, Fc, etc. as known in the art to enhance stability in vivo.

In certain embodiments, a Wnt surrogate direct activates canonical Wnt signaling through binding to one Fzd proteins and to LRP5/6, particularly by binding to these proteins on a cell surface, e.g. the surface of a human cell. The direct activation of Wnt signaling by a Wnt surrogate is in contrast to potentiation of Wnt signaling, which enhances activity only when native Wnt proteins are present.

Wnt surrogates of the present activate Wnt signaling, e.g., by mimicking the effect or activity of a Wnt protein binding to a frizzled protein. The ability of the Wnt surrogates of the invention to mimic the activity of Wnt can be confirmed by a number of assays. The Wnt surrogates typically initiate a reaction or activity that is similar to or the same as that initiated by the receptor's natural ligand. In particular, the Wnt surrogates of the invention enhance the canonical Wnt/β-catenin signaling pathway. As used herein, the term "enhances" refers to a measurable increase in the level of Wnt/β-catenin signaling compared with the level in the absence of a Wnt surrogate of the invention.

In certain embodiments, an antibody or antigen-binding fragment thereof disclosed herein inhibits Wnt pathway signaling. In particular embodiments, binding of an anti-Fzd antibody or antigen-binding fragment thereof blocks or inhibits the binding of endogenous Wnt to one Fzd receptor on a cell surface, thus reducing or inhibiting Wnt signaling.

Various methods are known in the art for measuring the level of canonical Wnt/β-catenin signaling. These include, but are not limited to assays that measure: Wnt/β-catenin target gene expression; TCF reporter gene expression; β-catenin stabilization; LRP phosphorylation; Axin translocation from cytoplasm to cell membrane and binding to LRP. The canonical Wnt/β-catenin signaling pathway ultimately leads to changes in gene expression through the transcription factors TCF7, TCF7L1, TCF7L2 (a.k.a. TCF4), and LEF. The transcriptional response to Wnt activation has been characterized in a number of cells and tissues. As such,

global transcriptional profiling by methods well known in the art can be used to assess Wnt/β-catenin signaling activation or inhibition.

Changes in Wnt-responsive gene expression are generally mediated by TCF and LEF transcription factors. A TCF reporter assay assesses changes in the transcription of TCF/LEF controlled genes to determine the level of Wnt/β-catenin signaling. A TCF reporter assay was first described by Korinek, V. et al., 1997. Also known as TOP/FOP this method involves the use of three copies of the optimal TCF motif CCTTTGATC, or three copies of the mutant motif CCTTTGGCC, upstream of a minimal c-Fos promoter driving luciferase expression (pTOPFl_ASH and pFOPFl_ASH, respectively) to determine the transactivational activity of endogenous p-catenin/TCF4. A higher ratio of these two reporter activities (TOP/FOP) indicates higher β-catenin/TCF4 activity, whereas a lower ratio of these two reporter activities indicates lower β-catenin/TCF4 activity.

Various other reporter transgenes that respond to Wnt signals exist intact in animals and therefore, effectively reflect endogenous Wnt signaling. These reporters are based on a multimerized TCF binding site, which drives expression of LacZ or GFP, which are readily detectable by methods known in the art. These reporter genes include: TOP-GAL, BAT-GAL, ins-TOPEGFP, ins-TOPGAL, LEF-EGFP, Axin2-LacZ, Axin2-d2EGFP, Lgr5tm1 (cre/ERT2), TOPdGFP.

The recruitment of dephosphorylated β-catenin to the membrane, stabilization and phosphorylation status of β-catenin, and translocation of β-catenin to the nucleus (Klapholz- Brown Z et al., PLoS One. 2(9) e945, 2007), in some cases mediated by complex formation with TCF transcription factors and TNIK are key steps in the Wnt signaling pathway. Stabilization is mediated by Disheveled family proteins that inhibit the "destruction" complex so that degradation of intracellular β-catenin is reduced, and translocation of β-catenin to the nucleus follows thereafter. Therefore, measuring the level and location of β-catenin in a cell is a good reflection of the level of Wnt/β-catenin signaling. A non-limiting example of such an assay is the "BioImage β-Catenin Redistribution Assay" (Thermo Scientific) which provides recombinant U20S cells that stably express human β-catenin fused to the C-terminus of enhanced green fluorescent protein (EGFP). Imaging and analysis is performed

with a fluorescence microscope or HCS platform allowing the levels and distribution of EGFP-β-catenin to be visualized.

Another way, in which the destruction complex is inhibited, is by removal of Axin by recruitment of Axin to the cytoplasmic tail of the Wnt co-receptor LRP. Axin has been shown to bind preferentially to a phosphorylated form of the LRP tail. Visualization of Axin translocation, for example with a GFP-Axin fusion protein, is therefore another method for assessing levels of Wnt/β-catenin signaling.

In certain embodiments, a Wnt signaling pathway agonist enhances or increases canonical Wnt pathway signaling, e.g., β-catenin signaling, by at least 30%, 35%, 40%, 45%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 150%, 200%, 250%, 300%, 400% or 500%, as compared to the β-catenin signaling induced by a neutral substance or negative control as measured in an assay described above, for example as measured in the TOPFlash assay. A negative control may be included in these assays. In particular embodiments, Wnt agonists may enhance β-catenin signaling by a factor of 2x, 5x, 10x, 100x, 1000x, 10000x or more as compared to the activity in the absence of the agonist when measured in an assay described above, for example when measured in the TOPFlash assay, or any of the other assays mentioned herein.

In certain embodiments, a Wnt signaling pathway antagonist or inhibitor inhibits or decreases canonical Wnt pathway signaling, e.g., β-catenin signaling, by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, or 100%, as compared to the β-catenin signaling observed in the presence of a neutral substance or negative control as measured in an assay described above, for example as measured in the TOPFlash assay. A positive control may be included in these assays.

"Wnt gene product" or "Wnt polypeptide" when used herein encompass native sequence Wnt polypeptides, Wnt polypeptide variants, Wnt polypeptide fragments and chimeric Wnt polypeptides. In particular embodiments, a Wnt polypeptide is a native human full length mature Wnt protein.

For example, human native sequence Wnt proteins of interest in the present application include the following: Wnt-1 (GenBank Accession No. NM_005430); Wnt-2 (GenBank Accession No. NM_003391); Wnt-2B (Wnt-13) (GenBank Accession No.

NM_004185 (isoform 1), NM_024494.2 (isoform 2)), Wnt-3 (RefSeq.: NM_030753), Wnt3a (GenBank Accession No. NM_033131), Wnt-4 (GenBank Accession No. NM_030761), Wnt-5A (GenBank Accession No. NM_003392), Wnt-5B (GenBank Accession No. NM_032642), Wnt-6 (GenBank Accession No. NM_006522), Wnt-7A (GenBank Accession No. NM_004625), Wnt- 7B (GenBank Accession No. NM_058238), Wnt-8A (GenBank Accession No. NM_058244), Wnt-8B (GenBank Accession No. NM_003393), Wnt-9A (Wnt- 14) (GenBank Accession No. NM_003395), Wnt-9B (Wnt-15) (GenBank Accession No. NM_003396), Wnt-1 OA (GenBank Accession No. NM_025216), Wnt-10B (GenBank Accession No. NM_003394), Wnt-11 (GenBank Accession No. NM_004626), Wnt- 16 (GenBank Accession No. NM_016087)). Although each member has varying degrees of sequence identity with the family, all encode small (i.e., 39-46 kD), acylated, palmitoylated, secreted glycoproteins that contain 23-24 conserved cysteine residues whose spacing is highly conserved (McMahon, A P et al., Trends Genet. 1992; 8: 236-242; Miller, J R. Genome Biol. 2002; 3(1): 3001.1-3001.15). Other native sequence Wnt polypeptides of interest include orthologs of the above from any mammal, including domestic and farm animals, and zoo, laboratory or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, rats, mice, frogs, zebra fish, fruit fly, worm, etc.

"Wnt pathway signaling" or "Wnt signaling" is used herein to refer to the mechanism by which a biologically active Wnt exerts its effects upon a cell to modulate a cell's activity. Wnt proteins modulate cell activity by binding to Wnt receptors, including proteins from the Frizzled (Fzd) family of proteins, proteins from the ROR family of proteins, the proteins LRP5, LRP6 from the LRP family of proteins, the protein FRL1/crypto, and the protein Derailed/Ryk. Once activated by Wnt binding, the Wnt receptor(s) will activate one or more intracellular signaling cascades. These include the canonical Wnt signaling pathway; the Wnt/planar cell polarity (Wnt/PCP) pathway; the Wnt-calcium (Wnt/Ca^{2+}) pathway (Giles, RH et al. (2003) Biochim Biophys Acta 1653, 1-24; Peifer, M. et al. (1994) Development 120: 369-380; Papkoff, J. et al (1996) Mol. Cell Biol. 16: 2128-2134; Veeman, M. T. et al. (2003) Dev. Cell 5: 367-377); and other Wnt signaling pathways as is well known in the art.

For example, activation of the canonical Wnt signaling pathway results in the inhibition of phosphorylation of the intracellular protein β-catenin, leading to an accumulation of β- catenin in the cytosol and its subsequent translocation to the nucleus where it interacts with transcription factors, e.g. TCF/LEF, to activate target genes. Activation of the Wnt/PCP pathway activates RhoA, c-Jun N-terminal kinase (JNK), and nemo-like kinase (NLK) signaling cascades to control such biological processes as tissue polarity and cell movement. Activation of the Wnt/Ca^{2+} by, for example, binding of Wnt-4, Wnt-5A or Wnt-11, elicits an intracellular release of calcium ions, which activates calcium sensitive enzymes like protein kinase C (PKC), calcium-calmodulin dependent kinase II (CamKII) or calcineurin (CaCN). By assaying for activity of the above signaling pathways, the biological activity of an antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, can be readily determined.

In certain embodiments, functional properties of anti-Fzd antibodies and antigen-binding fragments thereof may be assessed using a variety of methods known to the skilled person, including e.g., affinity/binding assays (for example, surface plasmon resonance, competitive inhibition assays), cytotoxicity assays, cell viability assays, cell proliferation or differentiation assays in response to a Wnt, cancer cell and/or tumor growth inhibition using *in vitro* or *in vivo* models, including but not limited to any described herein. Other assays may test the ability of antibodies described herein to block normal Wnt/Fzd-mediated responses. The antibodies and antigen-binding fragments thereof described herein may also be tested for effects on Fzd receptor internalization, *in vitro* and *in vivo* efficacy, *etc.* Such assays may be performed using well-established protocols known to the skilled person (see *e.g.*, Current Protocols in Molecular Biology (Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., NY, NY); Current Protocols in Immunology (Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober 2001 John Wiley & Sons, NY, NY); or commercially available kits.

In certain embodiments, a Fzd-binding antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, comprises one or more of the CDRs of the antibodies described herein. In this regard, it has been shown in some cases that the transfer of only the VHCDR3 of an antibody can be performed while still retaining desired

specific binding (Barbas *et al.*, *PNAS* (1995) 92: 2529-2533). See also, McLane *et al.*, *PNAS* (1995) 92:5214-5218, Barbas *et al.*, *J. Am. Chem. Soc.* (1994) 116:2161-2162.

Marks et al (*Bio/Technology*, 1992, 10:779-783) describe methods of producing repertoires of antibody variable domains in which consensus primers directed at or adjacent to the 5' end of the variable domain area are used in conjunction with consensus primers to the third framework region of human VH genes to provide a repertoire of VH variable domains lacking a CDR3. Marks et al further describe how this repertoire may be combined with a CDR3 of a particular antibody. Using analogous techniques, the CDR3-derived sequences of the presently described antibodies may be shuffled with repertoires of VH or VL domains lacking a CDR3, and the shuffled complete VH or VL domains combined with a cognate VL or VH domain to provide an antibody or antigen-binding fragment thereof that binds one Fzd receptor. The repertoire may then be displayed in a suitable host system such as the phage display system of WO92/01047 so that suitable antibodies or antigen-binding fragments thereof may be selected. A repertoire may consist of at least from about 10^4 individual members and upwards by several orders of magnitude, for example, to about from 10^6 to 10^8 or 10^{10} or more members. Analogous shuffling or combinatorial techniques are also disclosed by Stemmer (Nature, 1994, 370:389-391), who describes the technique in relation to a β-lactamase gene but observes that the approach may be used for the generation of antibodies.

A further alternative is to generate novel VH or VL regions carrying one or more CDR-derived sequences of the herein described invention embodiments using random mutagenesis of one or more selected VH and/or VL genes to generate mutations within the entire variable domain. Such a technique is described by Gram et al (1992, Proc. Natl. Acad. Sci., USA, 89:3576-3580), who used error-prone PCR. Another method which may be used is to direct mutagenesis to CDR regions of VH or VL genes. Such techniques are disclosed by Barbas et al., (1994, Proc. Natl. Acad. Sci., USA, 91:3809-3813) and Schier et al (1996, J. Mol. Biol. 263:551-567).

In certain embodiments, a specific VH and/or VL of the antibodies described herein may be used to screen a library of the complementary variable domain to

identify antibodies with desirable properties, such as increased affinity for one Fzd receptor. Such methods are described, for example, in Portolano *et al.*, J. Immunol. (1993) 150:880-887; Clarkson *et al.*, Nature (1991) 352:624-628.

Other methods may also be used to mix and match CDRs to identify antibodies having desired binding activity, such as binding to one Fzd receptor. For example: Klimka *et al.*, *British Journal of Cancer* (2000) 83: 252-260, describe a screening process using a mouse VL and a human VH library with CDR3 and FR4 retained from the mouse VH. After obtaining antibodies, the VH was screened against a human VL library to obtain antibodies that bound antigen. Beiboer *et al.*, J. Mol. Biol. (2000) 296:833-849 describe a screening process using an entire mouse heavy chain and a human light chain library. After obtaining antibodies, one VL was combined with a human VH library with the CDR3 of the mouse retained. Antibodies capable of binding antigen were obtained. Rader *et al.*, PNAS (1998) 95:8910-8915 describe a process similar to Beiboer et al above.

These just-described techniques are, in and of themselves, known as such in the art. The skilled person will, however, be able to use such techniques to obtain antibodies or antigen-binding fragments thereof according to several embodiments of the invention described herein, using routine methodology in the art.

Also disclosed herein is a method for obtaining an antibody or antigen binding domain specific for a Fzd receptor, the method comprising providing by way of addition, deletion, substitution or insertion of one or more amino acids in the amino acid sequence of a VH domain set out herein or a VH domain which is an amino acid sequence variant of the VH domain, optionally combining the VH domain thus provided with one or more VL domains, and testing the VH domain or VH/VL combination or combinations to identify a specific binding member or an antibody antigen binding domain specific for one Fzd receptor and optionally with one or more desired properties. The VL domains may have an amino acid sequence which is substantially as set out herein. An analogous method may be employed in which one or more sequence variants of a VL domain disclosed herein are combined with one or more VH domains.

In particular embodiments, anti-Fzd antibodies, and antigen-binding fragments thereof, are water soluble. By "water soluble" it is meant a composition that is soluble

in aqueous buffers in the absence of detergent, usually soluble at a concentration that provides a biologically effective dose of the polypeptide. Compositions that are water soluble form a substantially homogenous composition that has a specific activity that is at least about 5% that of the starting material from which it was purified, usually at least about 10%, 20%, or 30% that of the starting material, more usually about 40%, 50%, or 60% that of the starting material, and may be about 50%, about 90% or greater. Anti-Fzd antibodies and antigen-binding fragments thereof, including Wnt surrogates, of the present invention typically form a substantially homogeneous aqueous solution at concentrations of at least 25 μM and higher, e.g. at least 25 μM, 40 μM, or 50 μM, usually at least 60 μM, 70 μM, 80 μM, or 90 μM, sometimes as much as 100 μM, 120 μM, or 150 μM. In other words, compositions of the present invention typically form a substantially homogeneous aqueous solution at concentrations of about 0.1 mg/ml, about 0.5 mg/ml, of about 1 mg/ml or more.

An antigen or epitope that "specifically binds" or "preferentially binds" (used interchangeably herein) to an antibody or antigen-binding fragment thereof is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target antigen, e.g., a Fzd receptor, if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically or preferentially binds to the Fzd1 receptor is an antibody that binds to the Fzd1 receptor with greater affinity, avidity, more readily, and/or with greater duration than it binds to other Fzd receptors or non-Fzd proteins. It is also understood by reading this definition that, for example, an antibody (or moiety or epitope) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

In some embodiments the frizzled binding moiety is selective for one frizzled protein of interest, e.g. having a specificity for the one desired frizzled protein of at least 10-fold, 25-fold, 50-fold, 100-fold, 200-fold or more relative to other frizzled proteins. In some embodiments, any of the one or more Fzd binding regions of a Wnt surrogate molecule is monospecific and binds or specifically binds to a single Fzd receptor, e.g., only one of Fzd1, Fzd2, Fzd3, Fzd4, Fzd5, Fzd6, Fzd7, Fzd8, Fzd9, or Fzd10.

In some embodiments, a monospecific Fzd binding region binds to a region of an Fzd receptor that does not include the cysteine rich domain (CRD) of the Fzd receptor, or includes less than the entire CRD of the FZD receptor. As illustrated in FIG.3, sequences within the CRD show strong homology between the 10 Fzd receptors, with homologies being even higher between subfamily members. Accordingly, certain embodiments of the monospecific Fzd binding regions disclosed herein do not bind to the CRD, or bind only to a subset of the CRD.

In some embodiments, a Fzd binding region, e.g., a monospecific Fzd binding region, binds to an epitope comprising at least a portion of the extracellular domain after the CRD, referred to herein as the “hinge region” of a Fzd receptor (see FIG. 2A). In particular embodiments, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the epitope is present within the hinge region of a Fzd receptor.

As illustrated in FIG 3, the hinge regions of the extracellular domain of Fzd receptors show highly divergent sequences. Sequences of illustrative Fzd receptor hinge regions are set forth in SEQ ID NOs: 1-10 and in Table 1 below. In certain embodiments, the hinge region includes an amino acid sequence having at least 90%, at least 95%, at least 98%, or at least 99% identity to any of the sequences set forth in SEQ ID NOs: 1-10.

Table 1: Fzd hinge region sequences

SID NO:	Fzd	Hinge Region Sequence
1	Fzd1	CVGQNTSDKGTPTPSLLPEFWTSNPQHGGGGH RGGFPGGAGASERGKFSC

2	Fzd2	CVGQNHSEDGAPALLTTAPPPGLQPGAGGTPG GPGGGGAPPRYATLEHPFHC
3	Fzd3	CDEPYPRLVDLNLAGEPTEGAPVAVQRDYGFW C
4	Fzd4	CMEGPGDEEVPLPHKTPIQPGEEC
5	Fzd5	CMDYNRSEATTAPPRPFPAKPTLPGPPGAPAS GGEC
6	Fzd6	CDETVPVTFDPHTEFLGPQKKTEQVQRDIGFWC
7	Fzd7	CVGQNTSDGSGGAGGSPTAYPTAPYLPDPPFT AMSPSDGRGRLSFPFSC
8	Fzd8	CMDYNRTDLTTAAPSPPRRLPPPPPGEQPPSG SGHGRPPGARPPHRGGGRGGGGGDAA APPARGGGGGGKARPPGGGAAPC
9	Fzd9	CMEAPENATAGPAEPHKGLGMLPVAPRPARPP GDLGPGAGGSGTC
10	Fzd10	CMEAPNNGSDEPTRGSGLFPPLFRPQRPHSAQ EHPLKDGGPGRGGC

In some embodiments, a monospecific Fzd binding region binds to an epitope comprising at least a portion of an N-terminal region upstream of the CRD of the Fzd receptor (FIG. 1). In particular embodiments, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the epitope is present within the N-terminal region of a Fzd receptor.

In yet further embodiments, a monospecific Fzd binding region binds to an epitope comprising a portion of both the CRD and the hinge region (see Table 2, clones designated “ext”). In particular embodiments, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the epitope is present within the hinge region, while the remainder is within the CRD.

Immunological binding generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific, for example by way of illustration and not limitation, as a result of electrostatic, ionic, hydrophilic and/or hydrophobic attractions or repulsion, steric forces, hydrogen bonding, van der Waals forces, and other interactions. The strength or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_D) of the interaction, wherein a smaller K_D represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the

interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off} /K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_D. See, generally, Davies *et al.* (1990) *Annual Rev. Biochem. 59*:439-473. In certain embodiment, the anti-Fzd antibodies bind one Fzd receptor with a K_D of less than or equal to about 1 x 10^{-4} M, less than or equal to about 1 x 10^{-5} M, less than or equal to about 1 x 10^{-6} M, less than or equal to about 1 x 10^{-7} M, less than or equal to about 1 x 10^{-8} M, less than or equal to about 1 x 10^{-9} M, or at least about 1 x 10^{-10} M. In certain embodiments, the anti-Fzd antibodies described herein bind one Fzd receptor with a K_D of less than about 10,000 nM, less than about 1000 nM, less than about 100 nM, less than about 10 nM, less than about 1 nM or less than about 0.1 nM, and in some embodiments, the antibodies may have even higher affinity for one Fzd receptor. In certain embodiments, the anti-Fzd antibodies described herein have an affinity K_D of about 100, 150, 155, 160, 170, 175, 180, 185, 190, 191, 192, 193, 194, 195, 196, 197, 198 or 199 picomolar, and in some embodiments, the antibodies may have even higher affinity for one Fzd receptor.

An antibody or antigen-binding fragment thereof according to certain embodiments includes antibodies and antigen binding fragments thereof that compete for binding to one Fzd receptor with any antibody described herein which both (i) specifically binds to the one Fzd receptor and/or (ii) comprises a VH and/or VL domain (or a VH and/or VL CDR set) disclosed herein, or (iii) comprises a VH CDR3 disclosed herein, or a variant of any of these. Competition between antibodies may be assayed easily *in vitro*, for example using ELISA and/or by tagging a specific reporter molecule to one antibody which can be detected in the presence of other untagged antibodies, to enable identification of specific antibodies which bind the same epitope or an overlapping epitope. Thus, there is provided herein a specific antibody or antigen-binding fragment thereof, comprising a human antibody antigen-binding site which competes with an antibody described herein that binds to one Fzd receptor.

In this regard, as used herein, the terms “competes with”, "inhibits binding" and "blocks binding" (*e.g.*, referring to inhibition/blocking of binding of a Wnt to one Fzd receptor or referring to inhibition/blocking of binding of an anti-Fzd antibody to a Fzd receptor) are used interchangeably and encompass both partial and complete inhibition/blocking. The inhibition/blocking of a Wnt to one Fzd receptor preferably reduces or alters the normal level or type of cell signaling that occurs when the Wnt binds to the Fzd receptor without inhibition or blocking. Inhibition and blocking are also intended to include any measurable decrease in the binding of a Wnt to a Fzd receptor when in contact with an anti-Fzd antibody as disclosed herein as compared to the ligand not in contact with an anti-Fzd antibody, *e.g.*, the blocking of binding of the Wnt to the Fzd receptor by at least about 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%.

The constant regions of immunoglobulins show less sequence diversity than the variable regions, and are responsible for binding a number of natural proteins to elicit important biochemical events. In humans, there are five different classes of antibodies including IgA (which includes subclasses IgA1 and IgA2), IgD, IgE, IgG (which includes subclasses IgG1, IgG2, IgG3, and IgG4), and IgM. The distinguishing features between these antibody classes are their constant regions, although subtler differences may exist in the V region.

The Fc region of an antibody interacts with a number of Fc receptors and ligands, imparting an array of important functional capabilities referred to as effector functions. For IgG, the Fc region comprises Ig domains CH2 and CH3 and the N-terminal hinge leading into CH2. An important family of Fc receptors for the IgG class are the Fc gamma receptors (FcγRs). These receptors mediate communication between antibodies and the cellular arm of the immune system (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). In humans this protein family includes FcγRI (CD64), including isoforms FcγRIa, FcγRIb, and FcγRIc; FcγRII (CD32), including isoforms FcγRIIa (including allotypes H131 and R131), FcγRIIb (including FcγRIIb-1 and FcγRIIb-2), and FcγRIIc; and FcγRIII (CD16), including isoforms FcγRIIIa (including allotypes V158 and F158) and FcγRIIIb (including allotypes FcγRIIIb-NA1

and FcγRIIIb-NA2) (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). These receptors typically have an extracellular domain that mediates binding to Fc, a membrane spanning region, and an intracellular domain that may mediate some signaling event within the cell. These receptors are expressed in a variety of immune cells including monocytes, macrophages, neutrophils, dendritic cells, eosinophils, mast cells, platelets, B cells, large granular lymphocytes, Langerhans' cells, natural killer (NK) cells, and T cells. Formation of the Fc/FcγR complex recruits these effector cells to sites of bound antigen, typically resulting in signaling events within the cells and important subsequent immune responses such as release of inflammation mediators, B cell activation, endocytosis, phagocytosis, and cytotoxic attack.

The ability to mediate cytotoxic and phagocytic effector functions is a potential mechanism by which antibodies destroy targeted cells. The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause lysis of the target cell is referred to as antibody dependent cell-mediated cytotoxicity (ADCC) (Raghavan *et al.*, 1996, Annu Rev Cell Dev Biol 12:181-220; Ghetie *et al.*, 2000, Annu Rev Immunol 18:739-766; Ravetch *et al.*, 2001, Annu Rev Immunol 19:275-290). The cell-mediated reaction wherein nonspecific cytotoxic cells that express FcγRs recognize bound antibody on a target cell and subsequently cause phagocytosis of the target cell is referred to as antibody dependent cell-mediated phagocytosis (ADCP). All FcγRs bind the same region on Fc, at the N-terminal end of the Cg2 (CH2) domain and the preceding hinge. This interaction is well characterized structurally (Sondermann *et al.*, 2001, J Mol Biol 309:737-749), and several structures of the human Fc bound to the extracellular domain of human FcγRIIIb have been solved (pdb accession code 1E4K) (Sondermann *et al.*, 2000, Nature 406:267-273.) (pdb accession codes 1IIS and 1IIX) (Radaev *et al.*, 2001, J Biol Chem 276:16469-16477.)

The different IgG subclasses have different affinities for the FcγRs, with IgG1 and IgG3 typically binding substantially better to the receptors than IgG2 and IgG4 (Jefferis *et al.*, 2002, Immunol Lett 82:57-65). All FcγRs bind the same region on IgG Fc, yet with different affinities: the high affinity binder FcγRI has a K_d for IgG1 of 10^{-8} M^{-1}, whereas the low affinity receptors FcγRII and FcγRIII generally bind at 10^{-6} and 10^{-5} respectively. The extracellular domains of FcγRIIIa and FcγRIIIb are 96%

identical; however, FcγRIIIb does not have an intracellular signaling domain. Furthermore, whereas FcγRI, FcγRIIa/c, and FcγRIIIa are positive regulators of immune complex-triggered activation, characterized by having an intracellular domain that has an immunoreceptor tyrosine-based activation motif (ITAM), FcγRIIb has an immunoreceptor tyrosine-based inhibition motif (ITIM) and is therefore inhibitory. Thus the former are referred to as activation receptors, and FcγRIIb is referred to as an inhibitory receptor. The receptors also differ in expression pattern and levels on different immune cells. Yet another level of complexity is the existence of a number of FcγR polymorphisms in the human proteome. A particularly relevant polymorphism with clinical significance is V158/F158 FcγRIIIa. Human IgG1 binds with greater affinity to the V158 allotype than to the F158 allotype. This difference in affinity, and presumably its effect on ADCC and/or ADCP, has been shown to be a significant determinant of the efficacy of the anti-CD20 antibody rituximab (Rituxan®, a registered trademark of IDEC Pharmaceuticals Corporation). Subjects with the V158 allotype respond favorably to rituximab treatment; however, subjects with the lower affinity F158 allotype respond poorly (Cartron *et al.*, 2002, Blood 99:754-758). Approximately 10-20% of humans are V158/V158 homozygous, 45% are V158/F158 heterozygous, and 35-45% of humans are F158/F158 homozygous (Lehrnbecher *et al.*, 1999, Blood 94:4220-4232; Cartron *et al.*, 2002, Blood 99:754-758). Thus 80-90% of humans are poor responders, that is, they have at least one allele of the F158 FcγRIIIa.

The Fc region is also involved in activation of the complement cascade. In the classical complement pathway, C1 binds with its C1q subunits to Fc fragments of IgG or IgM, which has formed a complex with antigen(s). In certain embodiments of the invention, modifications to the Fc region comprise modifications that alter (either enhance or decrease) the ability of a Fzd-specific antibody as described herein to activate the complement system (see *e.g.*, U.S. Patent 7,740,847). To assess complement activation, a complement-dependent cytotoxicity (CDC) assay may be performed (See, *e.g.*, Gazzano-Santoro *et al.*, J. Immunol. Methods, 202:163 (1996)).

Thus in certain embodiments, the present invention provides anti-Fzd antibodies having a modified Fc region with altered functional properties, such as

reduced or enhanced CDC, ADCC, or ADCP activity, or enhanced binding affinity for a specific FcγR or increased serum half-life. Other modified Fc regions contemplated herein are described, for example, in issued U.S. Patents 7,317,091; 7,657,380; 7,662,925; 6,538,124; 6,528,624; 7,297,775; 7,364,731; Published U.S. Applications US2009092599; US20080131435; US20080138344; and published International Applications WO2006/105338; WO2004/063351; WO2006/088494; WO2007/024249.

In certain embodiments, the Fc region may be derived from any of a variety of different Fcs, including but not limited to, a wild-type or modified IgG1, IgG2, IgG3, IgG4 or other isotype, e.g., wild-type or modified human IgG1, human IgG2, human IgG3, human IgG4, human IgG4Pro (comprising a mutation in core hinge region that prevents the formation of IgG4 half molecules), human IgA, human IgE, human IgM, or the modified IgG1 referred to as IgG1 LALAPG. The L235A, P329G (LALA-PG) variant has been shown to eliminate complement binding and fixation as well as Fc-γ dependent antibody-dependent cell-mediated cytotoxity (ADCC) in both murine IgG2a and human IgG1. In particular embodiments of any of the IgG disclosed herein, the IgG comprises one or more of the following amino acid substitutions: N297G, N297A, N297E, L234A, L235A, or P236G.

Thus, in certain embodiments, antibody variable domains with the desired binding specificities are fused to immunoglobulin constant domain sequences. In certain embodiments, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at

least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant effect on the yield of the desired chain combination.

Antibodies of the present invention (and antigen-binding fragments and variants thereof) may also be modified to include an epitope tag or label, *e.g.*, for use in purification or diagnostic applications. There are many linking groups known in the art for making antibody conjugates, including, for example, those disclosed in U.S. Pat. No. 5,208,020 or EP Patent 0 425 235 B1, and Chari *et al.*, Cancer Research 52: 127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

In another contemplated embodiment, a Fzd-specific antibody or antigen-binding fragment thereof as described herein may be conjugated or operably linked to another therapeutic compound, referred to herein as a conjugate. The conjugate may be a cytotoxic agent, a chemotherapeutic agent, a cytokine, an anti-angiogenic agent, a tyrosine kinase inhibitor, a toxin, a radioisotope, or other therapeutically active agent. Chemotherapeutic agents, cytokines, anti-angiogenic agents, tyrosine kinase inhibitors, and other therapeutic agents have been described above, and all of these aforementioned therapeutic agents may find use as antibody conjugates.

Immunoconjugates may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl)hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particular coupling agents include N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP) (Carlsson *et al.*, Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) to provide for a disulfide linkage. The linker may be a “cleavable linker” facilitating release of one or more

cleavable components. For example, an acid-labile linker may be used (Cancer Research 52: 127-131 (1992); U.S. Pat. No. 5,208,020).

In certain embodiments, anti-LRP5/6 antibodies and antigen-binding fragments thereof are monoclonal antibodies. In certain embodiments, they are humanized.

The present invention further provides in certain embodiments an isolated nucleic acid encoding an antibody or antigen-binding fragment thereof as described herein, for instance, a nucleic acid that codes for one or more CDR or VH or VL domain as described herein. Nucleic acids include DNA and RNA. These and related embodiments may include polynucleotides encoding antibodies that bind one Fzd receptors as described herein. The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the isolated polynucleotide (1) is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, (2) is linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence.

The term "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a transcription control sequence "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

The term "control sequence" as used herein refers to polynucleotide sequences that can affect expression, processing or intracellular localization of coding sequences to which they are ligated or operably linked. The nature of such control sequences may depend upon the host organism. In particular embodiments, transcription control sequences for prokaryotes may include a promoter, ribosomal binding site, and transcription termination sequence. In other particular embodiments, transcription control sequences for eukaryotes may include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, transcription termination sequences and polyadenylation

sequences. In certain embodiments, "control sequences" can include leader sequences and/or fusion partner sequences.

The term "polynucleotide" as referred to herein means single-stranded or double-stranded nucleic acid polymers. In certain embodiments, the nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine, ribose modifications such as arabinoside and 2',3'-dideoxyribose and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate. The term "polynucleotide" specifically includes single and double stranded forms of DNA.

The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" includes oligonucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. See, *e.g.*, LaPlanche *et al.*, 1986, Nucl. Acids Res., 14:9081; Stec *et al.*, 1984, J. Am. Chem. Soc., 106:6077; Stein *et al.*, 1988, Nucl. Acids Res., 16:3209; Zon *et al.*, 1991, Anti-Cancer Drug Design, 6:539; Zon *et al.*, 1991, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, pp. 87-108 (F. Eckstein, Ed.), Oxford University Press, Oxford England; Stec et al., U.S. Pat. No. 5,151,510; Uhlmann and Peyman, 1990, Chemical Reviews, 90:543, the disclosures of which are hereby incorporated by reference for any purpose. An oligonucleotide can include a detectable label to enable detection of the oligonucleotide or hybridization thereof.

The term "vector" is used to refer to any molecule (*e.g.*, nucleic acid, plasmid, or virus) used to transfer coding information to a host cell. The term "expression vector" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control expression of inserted heterologous nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and RNA splicing, if introns are present.

As will be understood by those skilled in the art, polynucleotides may include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the skilled person.

As will be also recognized by the skilled artisan, polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide according to the present disclosure, and a polynucleotide may, but need not, be linked to other molecules and/or support materials. Polynucleotides may comprise a native sequence or may comprise a sequence that encodes a variant or derivative of such a sequence.

Therefore, according to these and related embodiments, the present disclosure also provides polynucleotides encoding the anti-Fzd antibodies and antigen-binding fragments thereof described herein. In certain embodiments, polynucleotides are provided that comprise some or all of a polynucleotide sequence encoding an antibody or antigen-binding fragment thereof as described herein and complements of such polynucleotides.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encodes an antibody as described herein. Some of these polynucleotides bear minimal sequence identity to the nucleotide sequence of the native or original polynucleotide sequence that encode antibodies that bind to a Fzd receptor. Nonetheless, polynucleotides that vary due to differences in codon usage are expressly contemplated by the present disclosure. In certain embodiments, sequences that have been codon-optimized for mammalian expression are specifically contemplated.

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, may be employed for the preparation of variants

and/or derivatives of the antibodies described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provide a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments, the inventors contemplate the mutagenesis of the polynucleotide sequences that encode an antibody disclosed herein, or an antigen-binding fragment thereof, to alter one or more properties of the encoded polypeptide, such as the binding affinity of the antibody or the antigen-binding fragment thereof, or the function of a particular Fc region, or the affinity of the Fc region for a particular FcγR. The techniques of site-specific mutagenesis are well-known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phages are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

In many embodiments, the nucleic acids encoding a subject monoclonal antibody are introduced directly into a host cell, and the cell incubated under conditions sufficient to induce expression of the encoded antibody. The antibodies of this disclosure are prepared using standard techniques well known to those of skill in the art in combination with the polypeptide and nucleic acid sequences provided herein. The polypeptide sequences may be used to determine appropriate nucleic acid sequences encoding the particular antibody disclosed thereby. The nucleic acid sequence may be optimized to reflect particular codon "preferences" for various expression systems according to standard methods well known to those of skill in the art.

According to certain related embodiments there is provided a recombinant host cell which comprises one or more constructs as described herein; a nucleic acid encoding any antibody, CDR, VH or VL domain, or antigen-binding fragment thereof; and a method of production of the encoded product, which method comprises expression from encoding nucleic acid therefor. Expression may conveniently be achieved by culturing under appropriate conditions recombinant host cells containing the nucleic acid. Following production by expression, an antibody or antigen-binding fragment thereof, may be isolated and/or purified using any suitable technique, and then used as desired.

Antibodies or antigen-binding fragments thereof as provided herein, and encoding nucleic acid molecules and vectors, may be isolated and/or purified, *e.g.* from their natural environment, in substantially pure or homogeneous form, or, in the case of nucleic acid, free or substantially free of nucleic acid or genes of origin other

than the sequence encoding a polypeptide with the desired function. Nucleic acid may comprise DNA or RNA and may be wholly or partially synthetic. Reference to a nucleotide sequence as set out herein encompasses a DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

Systems for cloning and expression of a polypeptide in a variety of different host cells are well known. Suitable host cells include bacteria, mammalian cells, yeast and baculovirus systems. Mammalian cell lines available in the art for expression of a heterologous polypeptide include Chinese hamster ovary cells, HeLa cells, baby hamster kidney cells, NSO mouse melanoma cells and many others. A common, preferred bacterial host is *E. coli*.

The expression of antibodies and antigen-binding fragments thereof in prokaryotic cells such as *E. coli* is well established in the art. For a review, see for example Pluckthun, A. Bio/Technology 9: 545-551 (1991). Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production of antibodies or antigen-binding fragments thereof, see recent reviews, for example Ref, M. E. (1993) Curr. Opinion Biotech. 4: 573-576; Trill J. J. *et al.* (1995) Curr. Opinion Biotech 6: 553-560.

Suitable vectors can be chosen or constructed, containing appropriate regulatory sequences, including promoter sequences, terminator sequences, polyadenylation sequences, enhancer sequences, marker genes and other sequences as appropriate. Vectors may be plasmids, viral *e.g.* phage, or phagemid, as appropriate. For further details see, for example, Molecular Cloning: a Laboratory Manual: 2nd edition, Sambrook *et al.*, 1989, Cold Spring Harbor Laboratory Press. Many known techniques and protocols for manipulation of nucleic acid, for example in preparation of nucleic acid constructs, mutagenesis, sequencing, introduction of DNA into cells and gene expression, and analysis of proteins, are described in detail in Current Protocols in Molecular Biology, Second Edition, Ausubel *et al.* eds., John Wiley & Sons, 1992, or subsequent updates thereto.

The term "host cell" is used to refer to a cell into which has been introduced, or which is capable of having introduced into it, a nucleic acid sequence encoding one or more of the herein described antibodies, and which further expresses or is

capable of expressing a selected gene of interest, such as a gene encoding any herein described antibody. The term includes the progeny of the parent cell, whether or not the progeny are identical in morphology or in genetic make-up to the original parent, so long as the selected gene is present. Accordingly there is also contemplated a method comprising introducing such nucleic acid into a host cell. The introduction may employ any available technique. For eukaryotic cells, suitable techniques may include calcium phosphate transfection, DEAE-Dextran, electroporation, liposome-mediated transfection and transduction using retrovirus or other virus, *e.g.* vaccinia or, for insect cells, baculovirus. For bacterial cells, suitable techniques may include calcium chloride transformation, electroporation and transfection using bacteriophage. The introduction may be followed by causing or allowing expression from the nucleic acid, *e.g.* by culturing host cells under conditions for expression of the gene. In one embodiment, the nucleic acid is integrated into the genome (*e.g.* chromosome) of the host cell. Integration may be promoted by inclusion of sequences which promote recombination with the genome, in accordance-with standard techniques.

The present invention also provides, in certain embodiments, a method which comprises using a construct as stated above in an expression system in order to express a particular polypeptide such as a Fzd-specific antibody as described herein. The term "transduction" is used to refer to the transfer of genes from one bacterium to another, usually by a phage. "Transduction" also refers to the acquisition and transfer of eukaryotic cellular sequences by retroviruses. The term "transfection" is used to refer to the uptake of foreign or exogenous DNA by a cell, and a cell has been "transfected" when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. See, *e.g.*, Graham *et al.*, 1973, Virology 52:456; Sambrook *et al.*, 2001, MOLECULAR CLONING, A LABORATORY MANUAL, Cold Spring Harbor Laboratories; Davis *et al.*, 1986, BASIC METHODS IN MOLECULAR BIOLOGY, Elsevier; and Chu *et al.*, 1981, Gene 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

The term "transformation" as used herein refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to

contain a new DNA. For example, a cell is transformed where it is genetically modified from its native state. Following transfection or transduction, the transforming DNA may recombine with that of the cell by physically integrating into a chromosome of the cell, or may be maintained transiently as an episomal element without being replicated, or may replicate independently as a plasmid. A cell is considered to have been stably transformed when the DNA is replicated with the division of the cell. The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by a human. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by a human.

The terms "polypeptide" "protein" and "peptide" and "glycoprotein" are used interchangeably and mean a polymer of amino acids not limited to any particular length. The term does not exclude modifications such as myristylation, sulfation, glycosylation, phosphorylation and addition or deletion of signal sequences. The terms "polypeptide" or "protein" means one or more chains of amino acids, wherein each chain comprises amino acids covalently linked by peptide bonds, and wherein said polypeptide or protein can comprise a plurality of chains non-covalently and/or covalently linked together by peptide bonds, having the sequence of native proteins, that is, proteins produced by naturally-occurring and specifically non-recombinant cells, or genetically-engineered or recombinant cells, and comprise molecules having the amino acid sequence of the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The terms "polypeptide" and "protein" specifically encompass the antibodies that bind to a Fzd receptor of the present disclosure, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of an anti-Fzd antibody. Thus, a "polypeptide" or a "protein" can comprise one (termed "a monomer") or a plurality (termed "a multimer") of amino acid chains.

The term "isolated protein" or “isolated antibody” referred to herein means that a subject protein or antibody is (1) is free of at least some other proteins with which it would typically be found in nature, (2) is essentially free of other proteins from the

same source, *e.g.*, from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is not associated (by covalent or noncovalent interaction) with portions of a protein with which the "isolated protein" is associated in nature, (6) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (7) does not occur in nature. Such an isolated protein can be encoded by genomic DNA, cDNA, mRNA or other RNA, of may be of synthetic origin, or any combination thereof. In certain embodiments, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its use (therapeutic, diagnostic, prophylactic, research or otherwise).

Amino acid sequence modification(s) of the antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. For example, amino acid sequence variants of an antibody may be prepared by introducing appropriate nucleotide changes into a polynucleotide that encodes the antibody, or a chain thereof, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution may be made to arrive at the final antibody, provided that the final construct possesses the desired characteristics (*e.g.*, high affinity binding to one Fzd receptor). The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites. Any of the variations and modifications described above for polypeptides of the present invention may be included in antibodies of the present invention.

The present disclosure provides variants of the antibodies and antigen-binding fragments thereof disclosed herein. In certain embodiments, such variant antibodies or antigen-binding fragments, or CDRs thereof, bind to one Fzd receptor at least about 50%, at least about 70%, and in certain embodiments, at least about 90% as well as an antibody sequence specifically set forth herein. In further embodiments, such variant antibodies or antigen-binding fragments, or CDRs

thereof, bind to one Fzd receptor with greater affinity than the antibodies set forth herein, for example, that bind quantitatively at least about 105%, 106%, 107%, 108%, 109%, or 110% as well as an antibody sequence specifically set forth herein.

In particular embodiments, the antibody or antigen-binding fragment thereof, e.g., a Fab, scFv, VHH or sdAb, or Wnt surrogate, may comprise: a) a heavy chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and/or b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., one Fzd receptors). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody or antigen-binding fragment thereof wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10, 11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See *e.g.*, Muller, 1998, Structure 6:1153-1167).

In particular embodiments, a subject antibody or antigen-binding fragments thereof, e.g., a Fab, scFv, VHH or sdAb, or Wnt surrogate, may have: a) a heavy chain variable region having an amino acid sequence that is at least 80% identical, at least 95% identical, at least 90%, at least 95% or at least 98% or 99% identical, to the heavy chain variable region of an anti-Fzd antibody or antigen-binding fragments thereof described herein; and/or b) a light chain variable region having an amino acid sequence that is at least 80% identical, at least 85%, at least 90%, at least 95% or at least 98% or 99% identical, to the light chain variable region of an anti-Fzd antibody

or antigen-binding fragments thereof described herein. The amino acid sequences of illustrative antigen-binding fragments thereof are set forth herein.

In particular embodiments, the antibody or antigen-binding fragment thereof, e.g., a Fab, scFv, VHH or sdAb, or Wnt surrogate, may comprise one, two or more, three or more, four or more, five or more, or six of the CDRs identified in Table 1 for any particular antibody.

A polypeptide has a certain percent "sequence identity" to another polypeptide, meaning that, when aligned, that percentage of amino acids are the same when comparing the two sequences. Sequence similarity can be determined in a number of different manners. To determine sequence identity, sequences can be aligned using the methods and computer programs, including BLAST, available over the world wide web at ncbi.nlm.nih.gov/BLAST/. Another alignment algorithm is FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wis., USA, a wholly owned subsidiary of Oxford Molecular Group, Inc. Other techniques for alignment are described in Methods in Enzymology, vol. 266: Computer Methods for Macromolecular Sequence Analysis (1996), ed. Doolittle, Academic Press, Inc., a division of Harcourt Brace & Co., San Diego, Calif., USA. Of particular interest are alignment programs that permit gaps in the sequence. The Smith-Waterman is one type of algorithm that permits gaps in sequence alignments. See Meth. Mol. Biol. 70: 173-187 (1997). Also, the GAP program using the Needleman and Wunsch alignment method can be utilized to align sequences. See J. Mol. Biol. 48: 443-453 (1970)

Of interest is the BestFit program using the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2: 482-489 (1981) to determine sequence identity. The gap generation penalty will generally range from 1 to 5, usually 2 to 4 and in many embodiments will be 3. The gap extension penalty will generally range from about 0.01 to 0.20 and in many instances will be 0.10. The program has default parameters determined by the sequences inputted to be compared. Preferably, the sequence identity is determined using the default parameters determined by the program. This program is available also from Genetics Computing Group (GCG) package, from Madison, Wis., USA.

Another program of interest is the FastDB algorithm. FastDB is described in Current Methods in Sequence Comparison and Analysis, Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp. 127-149, 1988, Alan R. Liss, Inc. Percent sequence identity is calculated by FastDB based upon the following parameters:
Mismatch Penalty: 1.00; Gap Penalty: 1.00; Gap Size Penalty: 0.33; and Joining Penalty: 30.0.

In particular embodiments, the antibody may comprise: a) a heavy chain variable region comprising: i. a CDR1 region that is identical in amino acid sequence to the heavy chain CDR1 region of a selected antibody described herein; ii. a CDR2 region that is identical in amino acid sequence to the heavy chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the heavy chain CDR3 region of the selected antibody; and b) a light chain variable domain comprising: i. a CDR1 region that is identical in amino acid sequence to the light chain CDR1 region of the selected antibody; ii. a CDR2 region that is identical in amino acid sequence to the light chain CDR2 region of the selected antibody; and iii. a CDR3 region that is identical in amino acid sequence to the light chain CDR3 region of the selected antibody; wherein the antibody specifically binds a selected target (e.g., Fzd receptor, such as Fzd1). In a further embodiment, the antibody, or antigen-binding fragment thereof, is a variant antibody wherein the variant comprises a heavy and light chain identical to the selected antibody except for up to 8, 9, 10, 11, 12, 13, 14, 15, or more amino acid substitutions in the CDR regions of the VH and VL regions. In this regard, there may be 1, 2, 3, 4, 5, 6, 7, 8, or in certain embodiments, 9, 10, 11, 12, 13, 14, 15 more amino acid substitutions in the CDR regions of the selected antibody. Substitutions may be in CDRs either in the VH and/or the VL regions. (See *e.g.*, Muller, 1998, Structure 6:1153-1167).

Determination of the three-dimensional structures of representative polypeptides (*e.g.*, variant Fzd-specific antibodies as provided herein, for instance, an antibody protein having an antigen-binding fragment as provided herein) may be made through routine methodologies such that substitution, addition, deletion or insertion of one amino acids with selected natural or non-natural amino acids can be

virtually modeled for purposes of determining whether a so derived structural variant retains the space-filling properties of presently disclosed species. *See,* for instance, Donate et al., 1994 *Prot. Sci.* 3:2378; Bradley et al., *Science* 309: 1868-1871 (2005); Schueler-Furman et al., *Science* 310:638 (2005); Dietz et al., *Proc. Nat. Acad. Sci. USA* 103:1244 (2006); Dodson et al., *Nature* 450:176 (2007); Qian et al., *Nature* 450:259 (2007); Raman *et al.* Science 327:1014-1018 (2010). Some additional non-limiting examples of computer algorithms that may be used for these and related embodiments, such as for rational design of Fzd-specific antibodies antigen-binding domains thereof as provided herein, include VMD which is a molecular visualization program for displaying, animating, and analyzing large biomolecular systems using 3-D graphics and built-in scripting (see the website for the Theoretical and Computational Biophysics Group, University of Illinois at Urbana-Champagne, at ks.uiuc.edu/Research/vmd/. Many other computer programs are known in the art and available to the skilled person and which allow for determining atomic dimensions from space-filling models (van der Waals radii) of energy-minimized conformations; GRID, which seeks to determine regions of high affinity for different chemical groups, thereby enhancing binding, Monte Carlo searches, which calculate mathematical alignment, and CHARMM (Brooks et al. (1983) *J. Comput. Chem.* 4:187-217) and AMBER (Weiner et al (1981) *J. Comput. Chem*. 106: 765), which assess force field calculations, and analysis (see also, Eisenfield et al. (1991) *Am. J. Physiol.* 261:C376-386; Lybrand (1991) *J. Pharm. Belg.* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ. Health Perspect.* 61:185-190; and Kini et al. (1991) *J. Biomol. Struct. Dyn.* 9:475-488). A variety of appropriate computational computer programs are also commercially available, such as from Schrödinger (Munich, Germany).

In particular embodiments, the disclosure provides antibodies or antigen-binding fragments thereof that bind to a region of one Fzd receptor at points described in Table 4.

The disclosure also provides antibodies and antigen-binding fragments thereof that bind to one Frizzled receptor at specific contact points, including any of those disclosed in Table 4, which indicates specific sets of contact points for binding of various anti-Fzd antibodies or fragments thereof.

In another embodiment of invention, the anti-Fzd antibodies and humanized versions thereof are derived from rabbit monoclonal antibodies, and in particular are generated using RabMAb® technology. These antibodies are advantageous as they require minimal sequence modifications, thereby facilitating retention of functional properties after humanization using mutational lineage guided (MLG) humanization technology (see e.g., U.S. Patent No. 7,462,697). Thus, illustrative methods for making the anti-Fzd antibodies of the present disclosure include the RabMab® rabbit monoclonal antibody technology described, for example, in U.S. Patents 5,675,063 and 7,429,487. In this regard, in certain embodiments, the anti-Fzd antibodies of the disclosure are produced in rabbits. In particular embodiments, a rabbit-derived immortal B-lymphocyte capable of fusion with a rabbit splenocyte is used to produce a hybrid cell that produces an antibody. The immortal B-lymphocyte does not detectably express endogenous immunoglobulin heavy chain and may contain, in certain embodiments, an altered immunoglobulin heavy chain-encoding gene.

Compositions

Pharmaceutical compositions comprising an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more Wnt polypeptides or Norrin polypeptides.

In further embodiments, pharmaceutical compositions comprising a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises one or more polynucleotides comprising a nucleic acid sequence encoding a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding

sequences. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In further embodiments, pharmaceutical compositions comprising an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient are also disclosed. In particular embodiments, the pharmaceutical composition further comprises an expression vector, e.g., a viral vector, comprising a polynucleotide comprising a nucleic acid sequence encoding a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide, e.g., expression cassette.

The present invention further contemplates a pharmaceutical composition comprising a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid encoding an anti-Fzd antibody or antigen-binding fragment thereof described herein and one or more pharmaceutically acceptable diluent, carrier, or excipient. In particular embodiments, the pharmaceutical composition further comprises a cell comprising an expression vector comprising a polynucleotide comprising a promoter operatively linked to a nucleic acid sequence encoding a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide, e.g., expression cassette and/or in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

The present disclosure contemplates pharmaceutical compositions comprising a first molecule for delivery of anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, as a first active agent and a second molecule for delivery of a Wnt polypeptide or Norrin polypeptide. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

The subject molecules, alone or in combination, can be combined with pharmaceutically-acceptable carriers, diluents, excipients and reagents useful in preparing a formulation that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for mammalian, e.g., human or primate, use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. Examples of such carriers, diluents and excipients include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Supplementary active compounds can also be incorporated into the formulations. Solutions or suspensions used for the formulations can include a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates; detergents such as Tween 20 to prevent aggregation; and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. In particular embodiments, the pharmaceutical compositions are sterile.

Pharmaceutical compositions may further include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile

injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, or phosphate buffered saline (PBS). In some cases, the composition is sterile and should be fluid to allow it to be drawn into a syringe and provided to a subject using a syringe. In certain embodiments, it is stable under the conditions of manufacture and storage and is preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be, e.g., a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the internal compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile solutions can be prepared by incorporating the anti-Fzd antibody or antigen-binding fragment thereof (or encoding polynucleotide or cell comprising the same) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

In one embodiment, the pharmaceutical compositions are prepared with carriers that will protect the antibody or antigen-binding fragment thereof against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible

polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art.

It may be advantageous to formulate the pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active antibody or antigen-binding fragment thereof calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms are dictated by and directly dependent on the unique characteristics of the antibody or antigen-binding fragment thereof and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active antibody or antigen-binding fragment thereof for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser, e.g. syringe, e.g. a prefilled syringe, together with instructions for administration.

The pharmaceutical compositions of the invention encompass any pharmaceutically acceptable salts, esters, or salts of such esters, or any other compound which, upon administration to an animal comprising a human, is capable of providing (directly or indirectly) the biologically active antibody or antigen-binding fragment thereof.

The present invention includes pharmaceutically acceptable salts of the anti-Fzd antibodies or antigen-binding fragments thereof, e.g., Wnt surrogates, described herein. The term “pharmaceutically acceptable salt” refers to physiologically and pharmaceutically acceptable salts of the compounds of the invention: i.e., salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects thereto. A variety of pharmaceutically acceptable salts are known in the art and described, e.g., in “Remington’s Pharmaceutical Sciences”,

17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the "Encyclopaedia of Pharmaceutical Technology", 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in J. Pharm. Sci. 66: 2 (1977). Also, for a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, 2002).

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Metals used as cations comprise sodium, potassium, magnesium, calcium, and the like. Amines comprise N-N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge et al., "Pharmaceutical Salts," J. Pharma Sci., 1977, 66, 119). The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

In some embodiments, the pharmaceutical composition provided herein comprise a therapeutically effective amount of an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, described herein in admixture with a pharmaceutically acceptable carrier, diluent and/or excipient, for example saline, phosphate buffered saline, phosphate and amino acids, polymers, polyols, sugar, buffers, preservatives and other proteins. Exemplary amino acids, polymers and sugars and the like are octylphenoxy polyethoxy ethanol compounds, polyethylene glycol monostearate compounds, polyoxyethylene sorbitan fatty acid esters, sucrose, fructose, dextrose, maltose, glucose, mannitol, dextran, sorbitol, inositol, galactitol, xylitol, lactose, trehalose, bovine or human serum albumin, citrate, acetate, Ringer's and Hank's solutions, cysteine, arginine, carnitine, alanine, glycine, lysine, valine, leucine, polyvinylpyrrolidone, polyethylene and glycol. Preferably, this formulation is stable for at least six months at 4º C.

In some embodiments, the pharmaceutical composition provided herein comprises a buffer, such as phosphate buffered saline (PBS) or sodium phosphate/sodium sulfate, tris buffer, glycine buffer, sterile water and other buffers known to the ordinarily skilled artisan such as those described by Good et al. (1966) Biochemistry 5:467. The pH of the buffer may be in the range of 6.5 to 7.75, preferably 7 to 7.5, and most preferably 7.2 to 7.4.

Methods of Use

The present disclosure also provides methods for using the Fzd-specific antibodies, antigen-binding fragments thereof, e.g., Wnt surrogates, disclosed herein, e.g., to modulate a Wnt signaling pathway, e.g., to increase or decrease Wnt signaling, and the administration of Fzd-specific antibodies, antigen-binding fragments thereof, and Wnt surrogates disclosed herein in a variety of therapeutic settings. Provided herein are methods of treatment using the antibodies that bind one Fzd receptors or antigen-binding fragments thereof. In one embodiment, an antibody, or antigen-binding fragment thereof, of the present invention is provided to a subject having a disease involving inappropriate or deregulated Wnt signaling, e.g., increased or reduced Wnt signaling.

Increasing Wnt Pathway Signaling and Related Therapeutic Methods

In certain embodiments, an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may be used to increase Wnt signaling in a tissue or cell. Thus, in some aspects, the present invention provides a method for increasing Wnt signaling or enhancing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, disclosed herein, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway agonist. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro. In certain embodiments, the method comprises further contacting the tissue or cell with one or more Wnt polypeptides or Norrin polypeptides.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective

amount of a polynucleotide comprising an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, of the present invention. In certain embodiments, the target tissue or cell is also contacted with a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate. In certain embodiments, the tissue or cell is also contacted with a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same vector, e.g., in the same expression cassette.

In related aspects, the present invention provides a method for increasing Wnt signaling in a tissue, comprising contacting the tissue with an effective amount of a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, of the present invention. In certain embodiments, the tissue is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence

encoding the Wnt polypeptide or Norrin polypeptide are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Anti-Fzd antibodies and antigen-binding fragments thereof, e.g., Wnt surrogates, may be used in to treat a disease, disorder or condition, for example, by increasing Wnt signaling in a targeted cell, tissue or organ. Thus, in some aspects, the present invention provides a method for treating a disease or condition in a subject in need thereof, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting the subject with an effective amount of a composition of the present disclosure. In particular embodiments, the composition is a pharmaceutical composition comprising any of: an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate; a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate,, e.g., a DNA or mRNA, optionally a modified mRNA; a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate,, e.g., an expression vector or viral vector; or a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, e.g., a cell transduced with an expression vector or viral vector encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate. In particular embodiments, the disease or condition is a pathological disease or disorder, or an injury, e.g., an injury resulting from a wound. In certain embodiments, the wound may be the result of another therapeutic treatment. In certain embodiments, the disease or condition comprises impaired tissue repair, healing or regeneration, or would benefit from increased tissue repair, healing or regeneration. In some embodiments, contacting occurs in vivo, i.e., the subject composition is administered to a subject.

In certain embodiments, the method comprises further contacting the subject with a pharmaceutical composition comprising one or more Wnt polypeptides or Norrin polypeptides. The present disclosure contemplates contacting a subject with a first molecule for delivery of an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, as a first active agent and a second molecule for delivery of a Wnt polypeptide or Norrin polypeptide. The first and second molecule may be the same type of molecule or different types of molecules. For example, in certain embodiments, the first and second molecule may each be independently selected from the following types of molecules: polypeptides, small organic molecules, nucleic acids encoding the first or second active agent (optionally DNA or mRNA, optionally modified RNA), vectors comprising a nucleic acid sequence encoding the first or second active agent (optionally expression vectors or viral vectors), and cells comprising a nucleic acid sequence encoding the first or second active agent (optionally an expression cassette).

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, disclosed herein. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same polynucleotide.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate. In certain embodiments, the subject is also contacted with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same vector, e.g., in the same expression cassette.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with reduced Wnt signaling, or for which increased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate. In certain embodiments, the subject is also contacted with a cell comprising a nucleic acid sequence that encodes a Wnt polypeptide or a Norrin polypeptide. In certain embodiments, the nucleic acid sequence encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, and the nucleic acid sequence encoding the Wnt polypeptide or Norrin polypeptide are present in the same cell. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, or the Wnt polypeptide or Norrin polypeptide. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Wnt signaling plays key roles in the developmental process and maintenance of stem cells. Reactivation of Wnt signals is associated with regeneration and repair of most tissues after injuries and diseases. Anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, molecules are expected to provide benefit of healing and tissue repair in response to injuries and diseases. Causes of tissue damage and loss include but are not limited to aging, degeneration, hereditary conditions, infection and inflammation, traumatic injuries, toxins/metabolic-induced toxicities, or other pathological conditions. Wnt signals and enhancers of Wnt signals have been shown to activate adult, tissue-resident stem cells. In some embodiments, the compounds of the invention are administered for use in treating diseased or damaged tissue, for use in tissue regeneration and for use in cell growth and proliferation, and/or for use in tissue engineering.

Human diseases associated with mutations of the Wnt pathway provide strong evidence for enhancement of Wnt signals in the treatment and prevention of diseases. Preclinical in vivo and in vitro studies provide additional evidence of involvement of Wnt signals in many disease conditions and further support utilization of an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, in various human diseases.

Human diseases associated with mutations of the Wnt pathway provide strong evidence for enhancement of Wnt signals in the treatment and prevention of diseases. Preclinical in vivo and in vitro studies provide additional evidence of involvement of Wnt signals in many disease conditions and further support utilization of a Wnt surrogate molecule in various human diseases. For example, compositions of the present invention may be used to promote or increase bone growth or regeneration, bone grafting, healing of bone fractures, treatment of osteoporosis and osteoporotic fractures, spinal fusion, spinal cord injuries, including vertebral compression fractures, pre-operative spinal surgery optimization, osseointegration of orthopedic devices, tendon-bone integration, tooth growth and regeneration, dental implantation, periodontal diseases, maxillofacial reconstruction, and osteonecrosis of the jaw. They may also be used in the treatment of alopecia; enhancing regeneration of sensory organs, e.g. treatment of hearing loss, including regeneration of inner and outer auditory hair cells treatment of vestibular hypofunction, treatment of macular

degeneration, treatment of retinopathies, including vitreoretinopathy, diabetic retinopathy, other diseases of retinal degeneration, Fuchs' dystrophy, other cornea disease, etc.; treatment of stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, muscular dystrophy, muscle atrophy as a result of sarcopenia or cachexia, and other conditions affecting the degeneration or integrity of the blood brain barrier; . The compositions of this invention may also be used in treatment of oral mucositis, treatment of short bowel syndrome, inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), in particular CD with fistula formation, other gastrointestinal disorders; treatment of metabolic syndrome, dyslipidemia, treatment of diabetes, treatment of pancreatitis, conditions where exocrine or endocrine pancreas tissues are damaged; conditions where enhanced epidermal regeneration is desired, e.g., epidermal wound healing, treatment of diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, etc., conditions where angiogenesis is beneficial; treatment of myocardial infarction, coronary artery disease, heart failure; enhanced growth of hematopoietic cells, e.g. enhancement of hematopoietic stem cell transplants from bone marrow, mobilized peripheral blood, treatment of immunodeficiencies, graft versus host diseases, etc.; treatment of acute kidney injuries, chronic kidney diseases; treatment of lung diseases, chronic obstructive pulmonary diseases (COPD), pulmonary fibrosis, including idiopathic pulmonary fibrosis, enhanced regeneration of lung tissues. The compositions of the present invention may also be used in enhanced regeneration of liver cells, e.g. liver regeneration, treatment of cirrhosis, enhancement of liver transplantations, treatment of acute liver failure, treatment of chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, alcoholic liver diseases,alcoholic hepatitis, non-alcoholic liver diseases with steatosis or steatohepatitis, and the like. The compositions of this invention may treat diseases and disorders including, without limitation, conditions in which regenerative cell growth is desired.

Human genetics involving loss-of-function or gain-of-function mutations in Wnt signaling components show strong evidence supporting enhancing Wnt signals for bone growth. Conditions in which enhanced bone growth is desired may include, without limitation, fractures, grafts, ingrowth around prosthetic devices, osteoporosis,

osteoporotic fractures, spinal fusion, vertebral compression fractures, pre-operative optimization for spinal surgeries, osteonecrosis of the jaw, dental implantation, periodontal diseases, maxillofacial reconstruction, and the like. An anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, enhances and promotes Wnt signals which are critical in promoting bone regeneration. Methods for regeneration of bone tissues benefit from administration of the compounds of the invention, which can be systemic or localized. In some embodiments, bone marrow cells are exposed to molecules of the invention, such that stem cells within that marrow become activated.

In some embodiments, bone regeneration is enhanced by contacting a responsive cell population, e.g. bone marrow, bone progenitor cells, bone stem cells, etc. with an effective dose of an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, disclosed herein. Methods for regeneration of bone tissues benefit from administration of the anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate disclosed herein, which can be systemic or localized. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include, without limitation, absorbable collagen sponges, ceramics, hydrogels, polymeric microspheres, nanoparticles, bone cements, and the like.

Compositions comprising one or more anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, disclosed herein can be used for the in vivo treatment of skeletal tissue deficiencies. By "skeletal tissue deficiency", it is meant a deficiency in bone or other skeletal connective tissue at any site where it is desired to restore the bone or connective tissue, no matter how the deficiency originated, e.g. whether as a result of surgical intervention, removal of tumor, ulceration, implant, fracture, or other traumatic or degenerative conditions. The compositions of the present invention can be used as part of a regimen for restoring cartilage function to a connective tissue, for the repair of defects or lesions in cartilage tissue such as degenerative wear and arthritis, trauma to the tissue, displacement of torn

meniscus, meniscectomy, a luxation of a joint by a torn ligament, malalignment of joints, bone fracture, or by hereditary disease.

An anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may also be used for treatment of periodontal diseases. Periodontal diseases are a leading cause of tooth loss and are linked to multiple systemic conditions. In some embodiments, tooth or underlying bone regeneration is enhanced by contacting a responsive cell population. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo, with subsequent implantation of the activated stem or progenitor cells. The molecule may be localized to the site of action, e.g. by loading onto a matrix, which is optionally biodegradable, and optionally provides for a sustained release of the active agent. Matrix carriers include, without limitation, absorbable collagen sponges, ceramics, hydrogels, bone cements, polymeric microspheres, nanoparticles, and the like.

Studies have shown that biology of Wnt signaling and R-spondins are capable of promoting sensory hair cell regeneration in the inner ear following injuries, aging, or degeneration. Loss of sensory hair cells in the inner ear involved in hearing loss or vestibular hypofunction may also benefit from the compositions of the invention. In the inner ear, the auditory organ houses mechanosensitive hair cells required for translating sound vibration to electric impulses. The vestibular organs, comprised of the semicircular canals (SSCs), the utricle, and the saccule, also contain sensory hair cells in order to detect head position and motion. Compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the ear for enhancement of auditory regeneration.

An anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may also be used in regeneration of retinal tissue. In the adult mammalian retina, Muller glia cells are capable of regenerating retinal cells, including photoreceptors, for example after neurotoxic injury in vivo. Wnt signaling and enhancers of Wnt signals can promote proliferation of Muller glia-derived retinal progenitors after damage or during degeneration. The compositions of the invention may also be used in the regeneration of tissues and other cell types in the eye. For examples age-related macular degeneration (AMD), other retina degenerative

diseases, cornea diseases, Fuchs' dystrophy, vitreoretinopathy, hereditary diseases, etc. can benefit from the compositions of the present inventions. AMD is characterized by progressively decreased central vision and visual acuity. Fuchs' dystrophy is characterized by progressive loss of cornea endothelial cells. Wnt signal and enhancing of Wnt signal can promote regeneration of cornea endothelium, retina epithelium, etc. in the eye tissue. In other embodiments, compositions of the present invention can be used, for example, in an infusion; in a matrix or other depot system; or other topical application to the eye for retinal regeneration and treatment of macular degeneration.

Specific populations of proliferating cells for homeostatic renewal of hepatocytes have been identified through lineage tracing studies, for example Axin2-positive cells in peri-central region. Lineage tracing studies also identified additional potential liver progenitor cells, including but not limited to Lgr-positive cells. The self-renewing liver cells and other populations of potential progenitor cells, including Lgr5-positive and Axin2-positive cells, are identified to be capable of regeneration responding to Wnt signals and/or R-spondins following injuries. Numerous preclinical models of acute liver injury and failure and chronic liver diseases showed recovery and regeneration of hepatocytes benefit from enhancing Wnt signals. The compositions of this invention may be used in treatment of acute liver failure, acute alcoholic liver injuries, treatment of chronic liver diseases with hepatitis C or B virus infection or post-antiviral drug therapies, chronic alcoholic liver diseases, alcoholic hepatitis, non-alcoholic fatty liver diseases and non-alcoholic steatohepatitis (NASH), treatment of cirrhosis and severe chronic liver diseases of all causes, and enhanced regeneration of liver cells. Methods for regeneration of liver tissue benefit from administration of the compounds of the invention, which can be systemic or localized. These include, but are not limited to, methods of systemic administration and methods of localized administration e.g. by injection into the liver tissue, by injection into veins or blood vessels leading into the liver, by implantation of a sustained release formulation, and the like.

Wnt signals play an important role in regeneration of various epithelial tissues. Various epidermal conditions benefit from treatment with the compounds of the present invention. Mucositis occurs when there is a breakdown of the rapidly divided

epithelial cells lining the gastro-intestinal tract, leaving the mucosal tissue open to ulceration and infection. The part of the epithelial lining that covers the mouth, called the oral mucosa, is one of the most sensitive parts of the body and is particularly vulnerable to chemotherapy and radiation. Oral mucositis is probably the most common, debilitating complication of cancer treatments, particularly chemotherapy and radiation. In addition, the compositions of the invention may also benefit treatment of short bowel syndrome, inflammatory bowel diseases (IBD), or other gastrointestinal disorders. Other epidermal conditions include epidermal wound healing, diabetic foot ulcers, syndromes involving tooth, nail, or dermal hypoplasia, and the like. Molecules of the present invention may be used in all these conditions, where regenerative cells are contacted with compounds of the invention. Methods for regeneration of epithelial tissues benefit from administration of the compounds of the invention, which can be systemic or localized. Contacting can be, for example, topical, including intradermal, subdermal, in a gel, lotion, cream etc. applied at targeted site, etc.

In addition to skin and gastrointestinal tract, Wnt signals and enhancement and promotion of Wnt signals also play an important role in repair and regeneration of tissues including pancreas, kidney, and lung in preclinical models. An anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may benefit various disease conditions involving exocrine and endocrine pancreas, kidney, or lung. The anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may be used in treatment of metabolic syndrome; treatment of diabetes, treatment of acute or chronic pancreatitis, exocrine pancreatic insufficiency, treatment of acute kidney injuries, chronic kidney diseases, treatment of lung diseases, including but not limited to chronic obstructive pulmonary diseases (COPD), other conditions that cause loss of lung epithelial tissues. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

Epidermal Wnt signaling, in coordination with signaling via other development factors, is critical for adult hair follicle regeneration. Hair loss is a common problem, and androgenetic alopecia, often called male pattern baldness, is the most common form of hair loss in men. In some embodiments, hair follicle regeneration is

enhanced by contacting a responsive cell population with a molecule of the present invention. In some such embodiments, the contacting is performed in vivo. In other such embodiments, the contacting is performed ex vivo. The molecule may be localized to the site of action, e.g. topical lotions, gels, creams and the like.

Stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis and other conditions affecting the blood brain barrier (BBB) may be treated with an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate. Angiogenesis is critical to ensure the supply of oxygen and nutrients to many tissues throughout the body, and is especially important for the CNS as the neural tissue is extremely sensitive to hypoxia and ischemia. CNS endothelial cells which form the BBB differ from endothelial cells in non-neural tissue, in that they are highly polarized cells held together by tight junctions and express specific transporters. Wnt signaling regulates CNS vessel formation and/or function. Conditions in which the BBB is compromised can benefit from administration of the compounds of the invention, which can be systemic or localized e.g. by direct injection, intrathecal administration, implantation of sustained release formulations, and the like. In addition, Wnt signal is actively involved in neurogenesis and plays a role of neuroprotection following injury. The compositions of the present invention may also be used in treatment of spinal cord injuries, other spinal cord diseases, stroke, traumatic brain injuries, etc.

Wnt signals also play a role in angiogenesis. An anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, may benefit conditions where angiogenesis is beneficial, treatment of myocardial infarction, coronary artery disease, heart failure, diabetic retinopathy, etc., and conditions from hereditary diseases. Methods for regeneration of these tissues benefit from administration of the compounds of the invention, which can be systemic or localized.

In certain embodiments, methods of the present invention promote tissue regeneration, e.g., in a tissue subjected to damage or tissue or cell reduction or loss. The loss or damage can be anything which causes the cell number to diminish, including diseases or injuries. For example, an accident, an autoimmune disorder, a therapeutic side-effect or a disease state could constitute trauma. Tissue regeneration increases the cell number within the tissue and preferably enables

connections between cells of the tissue to be re-established, and more preferably the functionality of the tissue to be regained.

Reducing Wnt Pathway Signaling and Related Therapeutic Methods

In certain embodiments, an anti-Fzd antibody or antigen-binding fragment thereof, may be used to decrease or inhibit Wnt signaling in a tissue or cell. Thus, in some aspects, the present invention provides a method for decreasing Wnt signaling or inhibiting Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of an anti-Fzd antibody, or antigen-binding fragment thereof, disclosed herein, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In some embodiments, contacting occurs in vitro, ex vivo, or in vivo. In particular embodiments, the cell is a cultured cell, and the contacting occurs in vitro.

In related aspects, the present invention provides a method for decreasing or inhibiting Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a polynucleotide comprising an anti-Fzd antibody or antigen-binding fragment thereof, of the present invention, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences

In related aspects, the present invention provides a method for decreasing or inhibiting Wnt signaling in a tissue or cell, comprising contacting the tissue or cell with an effective amount of a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector.

In related aspects, the present invention provides a method for decreasing or inhibiting Wnt signaling in a tissue, comprising contacting the tissue with an effective

amount of a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the cell was transduced with a vector comprising an expression cassette encoding the anti-Fzd antibody or antigen-binding fragment thereof, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

Anti-Fzd antibodies and antigen-binding fragments thereof, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor, may be used in to treat a disease, disorder or condition, for example, by decreasing or inhibiting Wnt signaling in a cell, tissue or organ. Thus, in some aspects, the present invention provides a method for treating a disease or condition in a subject in need thereof, e.g., a disease or disorder associated with increased or deregulated Wnt signaling, or for which decreased Wnt signaling would provide a therapeutic benefit, comprising contacting the subject with an effective amount of a composition comprising an anti-Fzd antibody or antigen-binding fragment thereof, wherein the anti-Fzd antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In particular embodiments, the composition is a pharmaceutical composition comprising any of: an anti-Fzd antibody or antigen-binding fragment thereof; a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a DNA or mRNA, optionally a modified mRNA; a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., an expression vector or viral vector; or a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, e.g., a cell transduced with an expression vector or viral vector encoding an anti-Fzd antibody or antigen-binding fragment thereof. In particular embodiments, the disease or condition is a pathological disease or disorder, or an injury. In some embodiments, contacting occurs in vivo, i.e., the subject composition is administered to a subject.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with increased Wnt signaling, or for which reduced Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a polynucleotide comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor, disclosed herein. In certain embodiments, the polynucleotides are DNA or mRNA, e.g., a modified mRNA. In particular embodiments, the polynucleotides are modified mRNAs further comprising a 5' cap sequence and/or a 3' tailing sequence, e.g., a polyA tail. In other embodiments, the polynucleotides are expression cassettes comprising a promoter operatively linked to the coding sequences

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with increased Wnt signaling, or for which decreased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a vector comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In certain embodiments, the vector is an expression vector, and may comprise a promoter operatively linked to the nucleic acid sequence. In particular embodiments, the vector is a viral vector.

In related aspects, the present invention provides a method for treating a disease or condition, e.g., a disease or disorder associated with increased Wnt signaling, or for which decreased Wnt signaling would provide a therapeutic benefit, comprising contacting a subject in need thereof with a pharmaceutical composition comprising an effective amount of a cell comprising a nucleic acid sequence encoding an anti-Fzd antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof is a Wnt signaling pathway antagonist or inhibitor. In particular embodiments, the cell is a heterologous cell or an autologous cell obtained from the subject to be treated. In certain embodiments, the

cell was transduced with a vector comprising an expression cassette encoding the anti-Fzd antibody or antigen-binding fragment thereof. In particular embodiments, the cell is a stem cell, e.g., an adipose-derived stem cell or a hematopoietic stem cell.

In certain embodiments, methods of treating or preventing diseases or disorders in a subject in need thereof, by providing to the subject an effective amount of an anti-Fzd antibody, or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway, may be used to treat a cancer or tumor, e.g., a solid or liquid tumor. Examples of cancers and tumors that may be treated include, but are not limited to: colon tumors (e.g. colon cancer or adenoma), stomach tumors (e.g., stomach cancer), small intestine tumors (e.g., small intestinal cancer), liver tumors (e.g., liver cancer), pancreas tumors (e.g., pancreatic cancer), lung tumors (e.g., lung cancer), ovary tumors (e.g., ovarian cancer), kidney (e.g., kidney cancer), brain tumors (e.g., brain cancer), spinal cord tumors (e.g., spinal cord cancer), skin tumors (e.g., skin cancer or melanoma), head and neck tumors (e.g., head and neck cancer), gastointestinal tract tumors (e.g., gastrointestinal cancer, esophageal cancer, oral mucosa cancer, tongue cancer, stomach cancer, intestinal cancer, colon cancer), breast tumors (e.g., breast cancer), prostate tumors (e.g., prostate cancer), bone tumors (e.g., bone cancer), vascular tumors, Wilms tumor, leukemina/lymphoma, soft tissue tumors (e.g., soft tissue sarcoma or synovial sarcoma) and metastatic cancers, etc.

In certain embodiments, methods of treating or preventing diseases or disorders in a subject in need thereof, by providing to the subject an effective amount of an anti-Fzd antibody, or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway, may be used to treat degenerative diseases. Examples of degenerative diseases that may be treated include, but are not limited to osteoarthritis, cartilage degeneration, sports injuries (e.g., cartilage injury), retinopathy, atherosclerosis, neurodegenerative disorders, and vascular disorders e.g. vasculitis, conditions with abnormal angiogenesis.

In certain embodiments, methods of treating or preventing diseases or disorders in a subject in need thereof, by providing to the subject an effective amount of an anti-Fzd antibody, or an antigen-binding fragment thereof, wherein the antibody

or the antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway, may be used to treat fibrosis. Examples of fibrosis that may be treated include, but are not limited to, lung fibrosis (including but not limited to COPD and idiopathic pulmonary fibrosis), kidney fibrosis (e.g. end stage renal failure), liver fibrosis, congenital liver storage diseases, and cardiac fibrosis.

In certain embodiments, methods of treating or preventing diseases or disorders in a subject in need thereof, by providing to the subject an effective amount of an anti-Fzd antibody, or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway, may be used to treat heart failure, e.g., congestive heart failure, systolic heart failure, heart failure with preserved ejection fraction, or coronary artery disease.

In certain embodiments, methods of treating or preventing diseases or disorders in a subject in need thereof, by providing to the subject an effective amount of an anti-Fzd antibody, or an antigen-binding fragment thereof, wherein the antibody or the antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway, may be used to treat heterotopic ossification, osteopetrosis, or congenital high bone mass disorders.

The terms "administering" or "introducing" or “providing”, as used herein, refer to delivery of a composition to a cell, to cells, tissues and/or organs of a subject, or to a subject. Such administering or introducing may take place in vivo, in vitro or ex vivo.

In particular embodiments, a pharmaceutical composition is administered parenterally, e.g., intravenously, orally, rectally, or by injection. In some embodiments, it is administered locally, e.g., topically or intramuscularly. In some embodiments, a composition is administered to target tissues, e.g., to bone, joints, ear tissue, eye tissue, gastrointestinal tract, skin, a wound site or spinal cord. Methods of the invention may be practiced in vivo or ex vivo. In some embodiments, the contacting of a target cell or tissue with a tissue-specific Wnt signal enhancing molecule is performed ex vivo, with subsequent implantation of the cells or tissues, e.g., activated stem or progenitor cells, into the subject. The skilled artisan can determine an appropriate site of and route of administration based on the disease or disorder being treated.

The dose and dosage regimen may depend upon a variety of factors readily determined by a physician, such as the nature of the disease or disorder, the characteristics of the subject, and the subject's history. In particular embodiments, the amount of anti-Fzd antibody or antigen-binding fragment thereof, e.g., a Wnt surrogate, administered or provided to the subject is in the range of about 0.01 mg/kg to about 50 mg/kg, 0.1 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 50 mg/kg of the subject's body weight.

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof, e.g. reducing the likelihood that the disease or symptom thereof occurs in the subject, and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of a disease in a mammal, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; or (c) relieving the disease, i.e., causing regression of the disease. The therapeutic agent (e.g., anti-Fzd antibody or antigen-binding fragment thereof) may be administered before, during or after the onset of disease or injury. The treatment of ongoing disease, where the treatment stabilizes or reduces the undesirable clinical symptoms of the patient, is of particular interest. Such treatment is desirably performed prior to complete loss of function in the affected tissues. The subject therapy will desirably be administered during the symptomatic stage of the disease, and in some cases after the symptomatic stage of the disease. In some embodiments, the subject method results in a therapeutic benefit, e.g., preventing the development of a disorder, halting the progression of a disorder, reversing the progression of a disorder, etc. In some embodiments, the subject method comprises the step of detecting that a therapeutic benefit has been achieved. The ordinarily skilled artisan will appreciate that such measures of therapeutic efficacy will be applicable to the particular disease being modified, and will recognize the appropriate detection methods to use to measure therapeutic efficacy.

Promoting Cell, Tissue and Organoid Growth and Related Methods

Other embodiments relate, in part, to the use of the Wnt surrogate molecules disclosed herein to promote or enhance the growth or proliferation of cells, tissues and organoids, for example, by contacting cells or tissue with one or more Wnt surrogate, optionally in combination with a Norrin or Rspondin polypeptide. In certain embodiments, the cells or tissue are contacted ex vivo, in vitro, or in vivo. Such methods may be used to generate cells, tissue or organoids for therapeutic use, e.g., to be transplanted or grafted into a subject. They may also be used to generate cells, tissue or organoids for research use. The Wnt surrogate molecules have widespread applications in non-therapeutic methods, for example in vitro research methods.

The invention provides a method for tissue regeneration of damaged tissue, such as the tissues discussed above, comprising administering a Wnt surrogate molecule to cells. The Wnt surrogate molecule may be administered directly to the cells in vivo, administered to a subject orally, intravenously, or by other methods known in the art, or administered to ex vivo cells. In some embodiments where the Wnt surrogate molecule is administered to ex vivo cells, these cells may be transplanted into a subject before, after or during administration of the Wnt surrogate molecule.

Wnt signaling is a key component of stem cell culture. For example, the stem cell culture media as described in WO2010/090513, WO2012/014076, Sato et al., 2011 (GASTROENTEROLOGY 201 1; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5). The Wnt surrogate molecules disclosed herein are suitable alternatives to Rspondin for use in these stem cell culture media, or may be combined with Rspondin.

Accordingly, in one embodiment, the disclosure provides a method for enhancing the proliferation of stem cells comprising contacting stem cells with one or more Wnt surrogate molecules disclosed herein. In one embodiment, the disclosure provides a cell culture medium comprising one or more Wnt surrogate molecules disclosed herein. In some embodiments, the cell culture medium may be any cell culture medium already known in the art that normally comprises Wnt or Rspondin, but wherein the Wnt or Rspondin is replaced (wholly or partially) or supplemented by Wnt surrogate molecule(s) disclosed herein. For example, the culture medium may be as described in as described in WO2010/090513, WO2012/014076, Sato et al.,

2011 (GASTROENTEROLOGY 201 1; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5), which are hereby incorporated by reference in their entirety.

Stem cell culture media often comprise additional growth factors. This method may thus additionally comprise supplying the stem cells with a growth factor. Growth factors commonly used in cell culture medium include epidermal growth factor (EGF, (Peprotech), Transforming Growth Factor-alpha (TGF-alpha, Peprotech), basic Fibroblast Growth Factor (bFGF, Peprotech), brain-derived neurotrophic factor (BDNF, R&D Systems), Hepatocyte Growth Factor (HGF) and Keratinocyte Growth Factor (KGF, Peprotech, also known as FGF7). EGF is a potent mitogenic factor for a variety of cultured ectodermal and mesodermal cells and has a profound effect on the differentiation of specific cells in vivo and in vitro and of some fibroblasts in cell culture. The EGF precursor exists as a membrane-bound molecule which is proteolytically cleaved to generate the 53-amino acid peptide hormone that stimulates cells. EGF or other mitogenic growth factors may thus be supplied to the stem cells. During culturing of stem cells, the mitogenic growth factor may be added to the culture medium every second day, while the culture medium is refreshed preferably every fourth day. In general, a mitogenic factor is selected from the groups consisting of: i) EGF, TGF-alpha, and KGF, ii) EGF, TGF-alpha, and FGF7; iii) EGF, TGF-alpha, and FGF; iv) EGF and KGF; v) EGF and FGF7; vi) EGF and a FGF; vii) TGF-alpha and KGF; viii) TGF-alpha, and FGF7; ix) or from TGF-alpha and a FGF. In certain embdoiments, the disclosure includes a stem cell culture media comprising a Wnt surrogate molecule disclosed herein, e.g., optionally in combination with one or more of the growth factors or combinations thereof described herein.

These methods of enhancing proliferation of stem cells can be used to grow new organoids and tissues from stem cells, as for example described in WO2010/090513 WO2012/014076, Sato et al., 201 1 (GASTROENTEROLOGY 2011; 141: 1762-1772) and Sato et al., 2009 (Nature 459, 262-5).

In some embodiments, the Wnt surrogate molecules are used to enhance stem cell regeneration. Illustrative stem cells of interest include but are not limited to: muscle satellite cells; hematopoietic stem cells and progenitor cells derived therefrom (U.S. Pat. No. 5,061 ,620); neural stem cells (see Morrison et al. (1999)

Cell 96: 737-749); embryonic stem cells; mesenchymal stem cells; mesodermal stem cells; liver stem cells; adipose-tissue derived stem cells, etc.

Diagnostic and Related Methods

Other embodiments of the present invention relate, in part, to diagnostic applications for detecting the presence of cells or tissues expressing aFzd receptor. Thus, the present disclosure provides methods of detecting a Fzd receptor in a sample, such as detection of cells or tissues expressing Fzd1. Such methods can be applied in a variety of known detection formats, including, but not limited to immunohistochemistry (IHC), immunocytochemistry (ICC), *in situ* hybridization (ISH), whole-mount *in situ* hybridization (WISH), fluorescent DNA *in situ* hybridization (FISH), flow cytometry, enzyme immuno-assay (EIA), and enzyme linked immuno-assay (ELISA). In particular embodiments, a method comprises contacting a tissue or cell, e.g., obtained from a subject, with an antibody or antigen-binding fragment thereof disclosed herein, and then determining an amount of binding of the antibody or antigen-binding fragment thereof to the tissue or cell, thus determining the presence of or an amount of the Fzd receptor(s) in the tissue or cell.

ISH is a type of hybridization that uses a labeled complementary DNA or RNA strand (*i.e.*, primary binding agent) to localize a specific DNA or RNA sequence in a portion or section of a cell or tissue (*in situ*), or if the tissue is small enough, the entire tissue (whole mount ISH). One having ordinary skill in the art would appreciate that this is distinct from immunohistochemistry, which localizes proteins in tissue sections using an antibody as a primary binding agent. DNA ISH can be used on genomic DNA to determine the structure of chromosomes. Fluorescent DNA ISH (FISH) can, for example, be used in medical diagnostics to assess chromosomal integrity. RNA ISH (hybridization histochemistry) is used to measure and localize mRNAs and other transcripts within tissue sections or whole mounts.

In various embodiments, the antibodies and antigen-binding fragments thereof described herein are conjugated to a detectable label that may be detected directly or indirectly. In this regard, an antibody "conjugate" refers to an anti-Fzd antibody or antigen-binding fragment thereof that is covalently linked to a detectable label. In the present invention, DNA probes, RNA probes, monoclonal antibodies, antigen-binding

fragments thereof, and antibody derivatives thereof, such as a single-chain-variable-fragment antibody or an epitope tagged antibody, may all be covalently linked to a detectable label. In “direct detection”, only one detectable antibody is used, *i.e.*, a primary detectable antibody. Thus, direct detection means that the antibody that is conjugated to a detectable label may be detected, per se, without the need for the addition of a second antibody (secondary antibody).

A "detectable label" is a molecule or material that can produce a detectable (such as visually, electronically or otherwise) signal that indicates the presence and/or concentration of the label in a sample. When conjugated to an antibody, the detectable label can be used to locate and/or quantify the target to which the specific antibody is directed. Thereby, the presence and/or concentration of the target in a sample can be detected by detecting the signal produced by the detectable label. A detectable label can be detected directly or indirectly, and several different detectable labels conjugated to different specific-antibodies can be used in combination to detect one or more targets.

Examples of detectable labels, which may be detected directly, include fluorescent dyes and radioactive substances and metal particles. In contrast, indirect detection requires the application of one or more additional antibodies, *i.e.*, secondary antibodies, after application of the primary antibody. Thus, the detection is performed by the detection of the binding of the secondary antibody or binding agent to the primary detectable antibody. Examples of primary detectable binding agents or antibodies requiring addition of a secondary binding agent or antibody include enzymatic detectable binding agents and hapten detectable binding agents or antibodies.

In some embodiments, the detectable label is conjugated to a nucleic acid polymer which comprises the first binding agent (*e.g.*, in an ISH, WISH, or FISH process). In other embodiments, the detectable label is conjugated to an antibody which comprises the first binding agent (*e.g.*, in an IHC process).

Examples of detectable labels which may be conjugated to antibodies used in the methods of the present disclosure include fluorescent labels, enzyme labels, radioisotopes, chemiluminescent labels, electrochemiluminescent labels,

bioluminescent labels, polymers, polymer particles, metal particles, haptens, and dyes.

Examples of fluorescent labels include 5-(and 6)-carboxyfluorescein, 5- or 6-carboxyfluorescein, 6-(fluorescein)-5-(and 6)-carboxamido hexanoic acid, fluorescein isothiocyanate, rhodamine, tetramethylrhodamine, and dyes such as Cy2, Cy3, and Cy5, optionally substituted coumarin including AMCA, PerCP, phycobiliproteins including R-phycoerythrin (RPE) and allophycoerythrin (APC), Texas Red, Princeton Red, green fluorescent protein (GFP) and analogues thereof, and conjugates of R-phycoerythrin or allophycoerythrin, inorganic fluorescent labels such as particles based on semiconductor material like coated CdSe nanocrystallites.

Examples of polymer particle labels include micro particles or latex particles of polystyrene, PMMA or silica, which can be embedded with fluorescent dyes, or polymer micelles or capsules which contain dyes, enzymes or substrates.

Examples of metal particle labels include gold particles and coated gold particles, which can be converted by silver stains. Examples of haptens include DNP, fluorescein isothiocyanate (FITC), biotin, and digoxigenin. Examples of enzymatic labels include horseradish peroxidase (HRP), alkaline phosphatase (ALP or AP), β-galactosidase (GAL), glucose-6-phosphate dehydrogenase, β-N-acetylglucosamimidase, β-glucuronidase, invertase, Xanthine Oxidase, firefly luciferase and glucose oxidase (GO). Examples of commonly used substrates for horseradishperoxidase include 3,3'-diaminobenzidine (DAB), diaminobenzidine with nickel enhancement, 3-amino-9-ethylcarbazole (AEC), Benzidine dihydrochloride (BDHC), Hanker-Yates reagent (HYR), Indophane blue (IB), tetramethylbenzidine (TMB), 4-chloro-1-naphtol (CN), .alpha.-naphtol pyronin (.alpha.-NP), o-dianisidine (OD), 5-bromo-4-chloro-3-indolylphosp- hate (BCIP), Nitro blue tetrazolium (NBT), 2-(p-iodophenyl)-3-p-nitropheny- l-5-phenyl tetrazolium chloride (INT), tetranitro blue tetrazolium (TNBT), 5-bromo-4-chloro-3-indoxyl-beta-D-galactoside/ferro-ferricyanide (BCIG/FF).

Examples of commonly used substrates for Alkaline Phosphatase include Naphthol-AS-B 1-phosphate/fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-phosphate/- fast red TR (NABP/FR), Naphthol-AS-MX-phosphate/fast red TR (NAMP/FR), Naphthol-AS-B1-

phosphate/new fuschin (NABP/NF), bromochloroindolyl phosphate/nitroblue tetrazolium (BCIP/NBT), 5-Bromo-4-chloro-3-indolyl-b-- d-galactopyranoside (BCIG).

Examples of luminescent labels include luminol, isoluminol, acridinium esters, 1,2-dioxetanes and pyridopyridazines. Examples of electrochemiluminescent labels include ruthenium derivatives. Examples of radioactive labels include radioactive isotopes of iodide, cobalt, selenium, tritium, carbon, sulfur and phosphorous.

Detectable labels may be linked to the antibodies described herein or to any other molecule that specifically binds to a biological marker of interest, *e.g.*, an antibody, a nucleic acid probe, or a polymer. Furthermore, one of ordinary skill in the art would appreciate that detectable labels can also be conjugated to second, and/or third, and/or fourth, and/or fifth binding agents or antibodies, etc. Moreover, the skilled artisan would appreciate that each additional binding agent or antibody used to characterize a biological marker of interest may serve as a signal amplification step. The biological marker may be detected visually using, *e.g.*, light microscopy, fluorescent microscopy, electron microscopy where the detectable substance is for example a dye, a colloidal gold particle, a luminescent reagent. Visually detectable substances bound to a biological marker may also be detected using a spectrophotometer. Where the detectable substance is a radioactive isotope detection can be visually by autoradiography, or non-visually using a scintillation counter. See, *e.g.*, Larsson, 1988, Immunocytochemistry: Theory and Practice, (CRC Press, Boca Raton, Fla.); Methods in Molecular Biology, vol. 80 1998, John D. Pound (ed.) (Humana Press, Totowa, N.J.).

The invention further provides kits for detecting a Fzd receptor or cells or tissues expressing one or more Fzd receptors in a sample, wherein the kits contain at least one antibody, polypeptide, polynucleotide, vector or host cell as described herein. In certain embodiments, a kit may comprise buffers, enzymes, labels, substrates, beads or other surfaces to which the antibodies of the invention are attached, and the like, and instructions for use.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

EXAMPLES

EXAMPLE 1

CHARACTERIZATION OF ANTI-FZD ANTIBODIES

Antibody Fab, scFv and VHH or sdAb fragments disclosed herein were sequenced and sub-cloned into mammalian expression vectors for expression, purification, and characterization of binding affinities to various Fzd receptors.

Soluble recombinant proteins were prepared by transfection of respective expression vectors into Expi293F cells (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. Briefly, four days after the transfection, cell culture medium was collected after spin down the cell pellet. The media were incubated with either Protein A resin (REPLIGEN, Waltham, MA) for collecting proteins containing human IgG-Fc portion, or Nickel affinity resin (Roche, Basel, Switzerland) for collecting proteins conjugated with His-tag. Proteins were eluted with 10 mM glycine, pH 3.5 from Protein A resin, or with 150 mM imidazole, pH 7.4 from Nickel affinity resin, respectively.

Subsequently, the protein elutes were fractionated and further purified by size-exclusion chromatography (SEC). SEC was performed by a fast protein liquid chromatography using a Superdex 200 Increase 10/300 GL (GE Healthcare, Pittsburgh, PA) in HBS buffer (10 mM HEPES, 150 mM NaCl, pH7.4). Each protein was injected onto the column at a volume of 475 µl or 500 µl. The absorbance at 280 nm was monitored, and the 500 µl fractions of all elutes were collected. Each collected faction near main peak was further analyzed by SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE) to confirm the content. SDS-PAGE was performed using Tris-HCl 4-15% gel (Bio-Rad, Hercules, CA) under both non-reducing and reducing conditions. The samples were prepared in Laemmli sample buffer and heated at 100ºC for 5 min.

Protein concentrations were determined using a NanoDrop Spectrophotometer (Thermo Scientific) by the direct UV A280 method. The relationship of absorbance to protein concentration is linear based on Beer-Lamber equation, $A = \varepsilon l c$; A is the absorbance value, ε is the wavelength-dependent extinction coefficient, l is the path length in centimeters, and c is the protein concentration. The experimental extinction coefficients of all produced proteins were estimated by their amino acid sequences.

Table 2 provides the heavy chain CDRs (CDRH1, CDRH2, and CDRH3) and light chain CDRs (CDRL1, CDRL2, and CDRL3) for the indicated antibody clones. The Abgenesis software from Distributed Bio was used to map the specificity determining regions (SDRs) shown below, which include the Kabat definition of CDRs (Padlan et al. *FASEB J*. 9, 133-139 (1995)).

Table 2 also indicates the Fzd receptor the antibody fragment was shown to bind. Confirmation of the binding of theFzd receptor to which each clone was raised was determined by detection of phage-displayed antibody fragments bound to target antigen immobilized on Nunc Maxisorb microtiter plates (Thermo Fisher Scientific, Waltham, MA) by single-dose or dose-dependent ELISA. Detection of bound phage was determined calorimetrically by turnover of TMB substrate (Thermo Fisher Scientific, Waltham, MA) at 415 nm by anti-M13-HRP antibody (GE Healthcare, Pittsburgh, PA). Clones were identified as binding to a Fzd receptor when the fold OD 450 nm over background was greater than a threshold level.

Table 2: Clone IDs and CDR sequences for hinge specific ("L") or hinge (L) + CRD ("ext") binders. "CDRH" indicates heavy chain CDRs, and "CDRL" indicates light chain CDRs.

(heavy chain CDRs)

Clone ID	Antigen	CDRH1	CDRH1 SEQ ID	CDRH2	CDRH2 SEQ ID	CDRH3	CDRH3 SEQ ID	ELISA specificity
031S-A01	hFzd1ext	YTFTSYYMH	34	GVIKPSGGSTSYA	730	CARGGGVFDYW	1426	hFzd1L,2L,7L
032S-A01	hFzd1L	DTLSSYGIS	35	GWINPNSGGTNYA	731	CARHGHWYFDLW	1427	hFzd1L, mFzd1L
033S-A01	hFzd1L	GTFSSSAIS	36	GIINPSGGGTSYA	732	CARRRPIVNWNDLDAFDIW	1428	hFzd1L, mFzd1L
033S-B01	hFzd1L	GTFSRYGIS	37	GIINPSGGGTSYA	733	CAREGEYCSSTSCAREEVW	1429	hFzd1L, mFzd1L
033S-C01	hFzd1L	GTFSTYAFN	38	GIINPSGGSTSYA	734	CARREYSGYDHDAFDIW	1430	hFzd1L, mFzd1L
033S-E01	hFzd1L	GTFTYDYMH	39	GIINPSGGSTSYA	735	CARGGYSSSWYPAAEYFQHW	1431	hFzd1L, mFzd1L

033S-F01	hFzd1L	YSFTSYYMY	40	GGIIPIFGTANYA	736	CARRDIVVVPAAKMEGAFDIW	1432	hFzd1L, mFzd1L
033S-G01	hFzd1L	GSFTNYAIS	41	GIIKPSGDSTSYA	737	CASRAIFGVVENYYMDVW	1433	mFzd1L
033S-H01	hFzd1L	YTFTRYGMN	42	GIINPSGGSTSYA	738	CARVLYDGMDVW	1434	hFzd1L, mFzd1L
033S-B02	hFzd1L	DTFDTYAIS	43	GIINPSGGSTSYA	739	CARRAVAGIFDYW	1435	hFzd1L, mFzd1L
033S-C02	hFzd1L	GTFSNYAIS	44	GWMNPDSGHTGYA	740	CARRIVVVTGDHAFDIW	1436	hFzd1L, mFzd1L
033S-D02	hFzd1L	ITFTSSAVH	45	GIINPSGGSTSYA	741	CARRMVYAPYKDVW	1437	hFzd1L, mFzd1L
033S-E02	hFzd1L	GTFTSYAIS	46	GMINPSGGRTTYA	742	CAIRTIFGVVIDYW	1438	hFzd1L, mFzd1L
033S-F02	hFzd1L	GTFSNSIIN	47	GVINPSGGYTSYA	743	CARRIDSSGYSSRYFDLW	1439	hFzd1L, mFzd1L
033S-G02	hFzd1L	GTFSSYAIS	48	GIINPNDGNTRHA	744	CARRSSGWYEVDYW	1440	hFzd1L, mFzd1L
033S-H02	hFzd1L	YTFTSYYMH	49	GIINPNGGSTIYA	745	CAREVATISSDDAQYYFDYW	1441	hFzd1L, mFzd1L
033S-A03	hFzd1L	GTFSSYAIS	50	GGIIPIFGTANYA	746	CARRPLWWHVAGVYYMDVW	1442	hFzd1L, mFzd1L
033S-B03	hFzd1L	YTFTGQYMH	51	GGIIPIFGTAHYP	747	CARRSVAAGTPFTDYW	1443	hFzd1L, mFzd1L
034S-C01	hFzd1L	YDFTDHFVH	52	GGIIPIFGTANYA	748	CARRSMIAATDAFDMW	1444	hFzd1L, mFzd1L
033S-E03	hFzd1L	FTFTSSAVQ	53	GIINPSGGSTSYA	749	CARRSKYSSSSGNEYFDLW	1445	hFzd1L, mFzd1L
034S-E01	hFzd1L	FSFENYWMS	54	SSINNSGDTYYA	750	CARAFNGMDVW	1446	hFzd1L, mFzd1L
034S-F01	hFzd1L	GTFSNYAIS	55	GIINPSSGSTNYA	751	CAARRRWEPRRRDFDLW	1447	hFzd1L, mFzd1L
034S-H01	hFzd1L	YRFTDYYFY	56	GGINPNSGGTNYA	752	CTARDPTFRGPGMDVW	1448	hFzd1L, mFzd1L
034S-A02	hFzd1L	YIFTNYXIQ	57	GIINPDYGNTMYA	753	CASTGTTVTTRGNDYW	1449	hFzd1L, mFzd1L
034S-B02	hFzd1L	DTFTGYYIH	58	GIINPSGGSTSYA	754	CARASWFGEGRQNDPW	1450	hFzd1L, mFzd1L
034S-C02	hFzd1L	HTFSDXYMH	59	GIINPSSGRTYHA	755	CARGSGWKHAEYFQHW	1451	hFzd1L, mFzd1L
034S-E02	hFzd1L	HTFTGYYIH	60	GIINPSGGSTYHA	756	CARASGFGEGQHFHPW	1452	hFzd1L
034S-F02	hFzd1L	YPFIGQYLH	61	GGIIPISGTASYA	757	CARGVEPYYGMDVW	1453	hFzd1L
037S-D01	hFzd1L	GTFTSYYMH	62	GIINPSGGSTSYA	758	CARRRIAAAGVDAFDIW	1454	hFzd1L
037S-E01	hFzd1L	YTFTGYYVH	63	GGIIPMSGSPSYA	759	CARRRVAAHSTHDAFDIW	1455	hFzd1L
037S-F01	hFzd1L	YTFTSYYMH	64	GIINPSGGSTSYA	760	CARDLRSGYSYAWSPW	1456	hFzd1L
037S-G01	hFzd1L	YTFRRYGIS	65	GWINPNSGGTNYA	761	CARFYTAGDYW	1457	hFzd1L
037S-H01	hFzd1L	NNFGSYAIT	66	GIINPSGGSTRYA	762	CARRAYSSRDGMDVW	1458	hFzd1L
037S-A02	hFzd1L	YTFTYYHMH	67	GWINPNSGGTNLA	763	CARARGYRAFDIW	1459	hFzd1L
037S-B02	hFzd1L	YTFTNYAMH	68	GWMNPNSGNTGSA	764	CARDGQQLEAFQHW	1460	hFzd1L
032S-E01	mFzd1L	DTFTSYYMH	69	GIISPSGGTTAYA	765	CARRAYSSSWYGYDAFDIW	1461	hFzd1L, mFzd1L
032S-E01	mFzd1L	YTFTNHWMH	70	GWISASNGNTNYA	766	CARDDVDSNYVGGMDVW	1462	hFzd1L, mFzd1L
032S-F01	mFzd1L	YTFTNYYIH	71	GWISAYNGNTNYA	767	CARDTGTTRTYYYGMDVW	1463	mFzd1L
032S-C02	mFzd1L	YTFTSYDIN	72	GWMNPNSGNTGYA	768	CARDLDGMDVW	1464	mFzd1L
032S-E02	mFzd1L	YTFPAXYMH	73	GWISAYNGNTNYA	769	CARDTGPKSYSSNAYGMDVW	1465	mFzd1L

032S-G02	mFzd1L	YTFTGYYMH	74	GIINPGGGGTSYA	770	CARDSGSNGYSFDIW	1466	mFzd1L
031S-D01	hFzd2ext	FTFGDHALS	75	SAISGSGGSTYYA	771	CAKSRAAHGYFDYW	1467	hFzd1L,2L,7L
031S-E01	hFzd2ext	FTFSPYGMH	76	SSISSSSSYIYYA	772	CARAGGSVENLGGDYW	1468	hFzd1L,2L,7L
031S-F01	hFzd2ext	XTFTDYAMD	77	GWINPNSGNTGYA	773	CARYSSSWYAFDIW	1469	hFzd2L
031S-G01	hFzd2ext	DTFSRSVFS	78	GWISAYNGNTNYA	774	CARDYGDYTQSNDYW	1470	hFzd2L
031S-B02	hFzd2ext	FTFSSYXMS	79	SAIGGSGANAYYA	775	CVRDTNWAFDLW	1471	hFzd2L
034S-H02	hFzd2L	YTFTSYYMH	80	GWMNPNSGNTGYA	776	CARDGKSIAVAGLDYW	1472	hFzd2L
034S-F03	hFzd2L	YTFSSYYIH	81	GWMNPKSGNTGNA	777	CAREGRLSYGMDVW	1473	hFzd2L
034S-C09	hFzd2L	YTFTGYYMH	82	GKINPTGGSTSYA	778	CAREWFDPW	1474	hFzd2L, mFzd2L
034S-D09	hFzd2L	YTFTSYYMH	83	GIINPNGGNTSYA	779	CARERAGVLSYFDLW	1475	hFzd2L, mFzd2L
034S-E09	hFzd2L	FTFSSYXMS	84	SAIGGIGDSTYYA	780	CARDTDVALDYW	1476	hFzd2L, mFzd2L
034S-F09	hFzd2L	FTFSSYXMS	85	SAIGGIGDSTYYA	781	CARDTDVALDYW	1477	hFzd2L, mFzd2L
034S-A10	hFzd2L	YTFTGYYMH	86	GWMNPNTGNTGYA	782	CARDRVYGMDVW	1478	hFzd2L, mFzd2L
034S-D10	hFzd2L	YTFTSYGTS	87	GWMNPNSGNTVYA	783	CARDWDLLDYW	1479	hFzd2L, mFzd2L
034S-C11	hFzd2L	YTFTSYYMH	88	GWMNPNSGNTGYA	784	CAREPLWFGESSPHDYYGMDVW	1480	hFzd2L, mFzd2L
034S-C12	hFzd2L	YTFTSYHIH	89	GGIIPISGTAKYV	785	CARDSLRLGFDYW	1481	mFzd2L
034S-F12	hFzd2L	GTFSSYAIS	90	GGIIPSFGSAKYA	786	CARGMYDYVWGRYPKGFDPW	1482	mFzd2L
034S-G12	hFzd2L	YTFTGYYMH	91	GWMNPNTGNTGYA	787	CARDRVYGMDVW	1483	mFzd2L
035S-D01	hFzd2L	YTFTSYYMH	92	GIINPSGGSTSYA	788	CARERAGVLSYFDLW	1484	mFzd2L
036S-A01	hFzd2L	RTFSIKPMG	93	ATIGSGALTNYA	789	CNTVPPTTYHSGTFFPEGYW	1485	hFzd2L, mFzd2L
037S-C02	hFzd2L	YTFTGYYMH	94	GKINZTGGSTZYA	790	CAREWFDPW	1486	hFzd2L
037S-G02	hFzd2L	FTFSDHYMS	95	SAIDNSGHRTWYA	791	CATDNERAFDIW	1487	hFzd2L
037S-A03	hFzd2L	YTFTTYYLH	96	GIINPNGGSTSYA	792	CAKENSYGMDVW	1488	hFzd2L
037S-C03	hFzd2L	YTFTGYPIH	97	GWISGYNGNTNYA	793	CARDSAGTTGYYYYGMDVW	1489	hFzd2L
037S-D03	hFzd2L	YTFTSYYMH	98	GIINPSGGSTSYA	794	CARAHWNYQGDAFDIW	1490	hFzd2L
037S-E03	hFzd2L	YTFTGYYMH	99	GKINPTGGSTZYA	795	CAREWFDPW	1491	hFzd2L
037S-H03	hFzd2L	YTFTGYYVH	100	GGIIPMSGSPSYA	796	CARRRVAAHSTHDAFDIW	1492	hFzd2L
037S-B04	hFzd2L	YTZTSYYMH	101	GWMNPNSGNTGYA	797	CAREKLGLGSGYFDYW	1493	hFzd2L
037S-F04	hFzd2L	YTFTSYYMH	102	GWMNPDSGDTGYA	798	CARDQEDYYGMDVW	1494	hFzd2L
037S-H04	hFzd2L	GTFSSYAIS	103	GWINPNSGGTNYA	799	CARNYYGSGSYIDYW	1495	hFzd2L, mFzd2L
037S-F05	hFzd2L	YTFTGYYMH	104	GWMSPASGNTGYA	800	CARDTDQWEHGYFDLW	1496	hFzd2L
048S-E01	hFzd2L	YTFTSYYMH	105	GWMNPNSGNTGYA	801	CARELGSGSYLSGYYYYGMDVW	1497	hFzd2L
048S-C01	hFzd2L	GTFSSYAIS	106	GWISGYNGNTNYA	802	CAREALRHYYYGMDVW	1498	hFzd2L
048S-G01	hFzd2L	YTFTHYYMH	107	GWINPNGGNTSYA	803	CARENVNSGFYYYGMDVW	1499	hFzd2L

048S-D01	hFzd2L	YTLTHYYMH	108	GWMNPNSGNTGYA	804	CARETVSSGYYYYGMDVW	1500	hFzd2L
048S-B02	hFzd2L	YTFTGYYMH	109	GKINPTGGSTSYA	805	CAREWFDPW	1501	hFzd2L
048S-F01	hFzd2L	YTFTGTYMH	110	GWISAYNGNTNYA	806	CARDTAVAGIDYW	1502	hFzd2L
048S-H01	hFzd2L	YTFTSYYMH	111	GWMNPDSGDTGYA	807	CARDQEDYYGMDVW	1503	hFzd2L
048S-A02	hFzd2L	FTFSSSWMH	112	SAISFSGGSTYYA	808	CARSYGDYGFDYW	1504	hFzd2L
048S-C02	hFzd2L	YSFNGYYMH	113	GWINPKSGGTTYA	809	CASEYSSPRGGVGMDVW	1505	hFzd2L
048S-E02	hFzd2L	FTFSSYGMH	114	SYITGSGSTRYYA	810	CARRQYCSSTSCYYGMDVW	1506	hFzd2L
048S-A01	hFzd2L	YTFSSYYIH	115	GWMNPKSGNTGNA	811	CAREGRLSYGMDVW	1507	hFzd2L, mFzd2L
049S-A01	hFzd2L	FZZSSYXMS	116	SAIGGIGDSTYYA	812	CARDTDVALDYW	1508	hFzd2L, mFzd2L
049S-C01	hFzd2L	YTFTKDYMH	117	GWMNPSSGNTGYA	813	CAREKVTPHYYYYYGMDVW	1509	hFzd2L, mFzd2L
049S-D01	hFzd2L	FAFSSYXMN	118	STISGGGVSTYYA	814	CAREDSSSWYAFDYW	1510	hFzd2L, mFzd2L
049S-E01	hFzd2L	YTFTGYYMH	119	GWMNPNTGNTGYA	815	CARDRVYGMDVW	1511	hFzd2L, mFzd2L
044S-G10	mFzd3L	YTFTTYYMH	120	GIINPSGGSTRYA	816	CARLPTNDYGDYVDYW	1512	hFzd3L, hFzd6L
044S-H10	mFzd3L	YTFTSYYMH	121	GIINPSGGSTSYA	817	CARIGYW	1513	mFzd3L
044S-A11	mFzd3L	GTFTRYTMH	122	GWMNPNSGNTAYA	818	CASQDVW	1514	mFzd3L
044S-B11	mFzd3L	DTFSTYAIS	123	GWMNPNSGKTGYA	819	CAKASGGAVLDYW	1515	hFzd3L, mFzd3L
044S-C11	mFzd3L	FTFSNAWMS	124	SAISRGGDNTYYA	820	CAREEGLWFRELSYYYYGMDVW	1516	hFzd3L, hFzd6L
044S-E11	mFzd3L	GTFSSYAIS	125	GWMNPTNGNTGYA	821	CASSRRHYGMDVW	1517	hFzd3L, hFzd6L
044S-F11	mFzd3L	FRFSDYSMN	126	SSISGSGGYTYYA	822	CARGPLCSGGSCYYYGMDVW	1518	hFzd3L, mFzd3L
044S-G11	mFzd3L	GTFSSYAIS	127	GWMNPNSGNTGYA	823	CARDGGYDALVGYYYGMDVW	1519	hFzd3L, mFzd3L
044S-H11	mFzd3L	YTFTGHYMH	128	GWISAYNGNTNYA	824	CAARGYW	1520	hFzd3L, mFzd3L
044S-B12	mFzd3L	FTFKEHGMH	129	SYISSGSSYIYYA	825	CAKQPYRGSGMDVW	1521	hFzd3L, mFzd3L
044S-C12	mFzd3L	GTFSSYAIS	130	GWMNPNSGNTGYA	826	CATDSLLAAAGTDYYYGMDVW	1522	hFzd3L, mFzd3L
044S-D12	mFzd3L	YAFTSYYMH	131	GIINPSGGSTIYA	827	CARGPWLHGFDYW	1523	hFzd3L, hFzd6L
044S-E12	mFzd3L	YTFTGYYMH	132	GVINPSGGGRTYA	828	CARGPLIRFHYYYGMDVW	1524	hFzd3L, mFzd3L
044S-F12	mFzd3L	GTFNSYAIS	133	GWINPASGGTKYA	829	CASTTTVASMDVW	1525	hFzd3L, hFzd6L
045S-A01	mFzd3L	GTFSSYAIN	134	GWMNPNSGNTGYA	830	CARVIYRENSGWSDFDYW	1526	hFzd3L, mFzd3L
045S-B01	mFzd3L	FTFSNHYTS	135	SAISTGGGTTYYA	831	CARDLGGYGMDVW	1527	hFzd3L, hFzd6L
045S-C01	mFzd3L	YTFTSYHMH	136	GWINPNSGGTNYA	832	CATRQAW	1528	hFzd3L, mFzd3L
045S-D01	mFzd3L	GTFSNYGVS	137	GRINPNSGNTGYA	833	CRGRFDPW	1529	hFzd3L, mFzd3L
045S-E01	mFzd3L	YPFTNNYIH	138	GWISPHSGRTRYA	834	CARDRTRYGMDVW	1530	hFzd3L, mFzd3L
045S-G01	mFzd3L	DTFTKYAIH	139	GWMNPNSGNTGYA	835	CARDRVVPAATYYYYYMDVW	1531	hFzd3L, mFzd3L
045S-H01	mFzd3L	GTFSSYAIS	140	GWMNPNSGNTGYG	836	CARVKGGSGWKRYFDLW	1532	hFzd3L, mFzd3L
045S-A02	mFzd3L	YTFTGHYLH	141	GWMNPSSGNTGYA	837	CARDWYGSGSYYSGDYYMDVW	1533	hFzd3L, mFzd3L

045S-B02	mFzd3L	GTFTAYYLH	142	GWMNPNSGNTGYA	838	CAREGYDILTGPGGMDVW	1534	hFzd3L, mFzd3L
045S-D02	mFzd3L	YTFTGYFIH	143	GRISGYNGNTNYA	839	CARGQSGIW	1535	hFzd3L, mFzd3L
045S-E02	mFzd3L	GTFSSYAIS	144	GWMNPNSGNAGYA	840	CARTLYSSGWARYFDLW	1536	hFzd3L, mFzd3L
045S-F02	mFzd3L	GTFDNYAIS	145	GWMNPNSGNTGLV	841	CARTPRVAGTFDYW	1537	hFzd3L, mFzd3L
045S-G02	mFzd3L	GTFSNYAIN	146	GWMNPNSGNTGSA	842	CASSSYSSGWYPIQHW	1538	hFzd3L, mFzd3L
045S-H02	mFzd3L	GTFSNYAIS	147	GIVDPMTGSTSYA	843	CARSRGVLWARGIDYW	1539	hFzd3L, mFzd3L
045S-A03	mFzd3L	FTFSNSDMN	148	SSISSSGGSTYYA	844	CARDLIMDVW	1540	hFzd3L, mFzd3L
045S-B03	mFzd3L	FTFSPYAMH	149	SAISGSGGSTYYA	845	CARENYGMDVW	1541	hFzd3L, mFzd3L
045S-C03	mFzd3L	FTFSSYAMH	150	SAISGSGGSTYYA	846	CASRGTGYSSSFDYW	1542	hFzd3L, mFzd3L
045S-D03	mFzd3L	GTFSSYAIS	151	GWISAYSGNTKYA	847	CARGRVATEKHWYFDLW	1543	hFzd3L, mFzd3L
045S-F03	mFzd3L	GTFSRNGIS	152	GWINSNNGETDFA	848	CARGGYW	1544	hFzd3L, mFzd3L
045S-G03	mFzd3L	GTFRSHVIS	153	GWMNPNSGYTGYA	849	CARSRDYGGNSAVGYW	1545	hFzd3L, mFzd3L
045S-H03	mFzd3L	YTFNSYYVH	154	GWINPNTGGTNFA	850	CARGRGNRGYSYGYEAVADDYW	1546	hFzd3L, mFzd3L
045S-A04	mFzd3L	DTFSHYAFS	155	GWISAYNGNTKYA	851	CARESGYDPYYGMDVW	1547	hFzd3L, hFzd6L
045S-B04	mFzd3L	DTFDTYAIS	156	GWMNRNSGNTGYA	852	CARHLNLAARREGFWYFDLW	1548	hFzd3L, mFzd3L
045S-D04	mFzd3L	YTFTSYYMH	157	GSINTGGGGTTYA	853	CATGRVRDYW	1549	hFzd3L, mFzd3L
045S-E04	mFzd3L	FTFSSYGMH	158	AVISHDGRKKYYA	854	CAGGSYSYDYW	1550	hFzd3L, mFzd3L
045S-F04	mFzd3L	YSFTRYHMH	159	GWINPNSGGTNYA	855	CARGQSGIW	1551	hFzd3L, mFzd3L
045S-G04	mFzd3L	GRFSRYAIS	160	GWINPNSGNTGNA	856	CARLDYYYGMDVW	1552	hFzd3L, mFzd3L
045S-H04	mFzd3L	GTFSSYPIS	161	GWMNPNSGNTGYA	857	CARSHSSSLLDYW	1553	hFzd3L, mFzd3L
045S-A05	mFzd3L	FTFSSYXMS	162	SVISGSGGSTYYA	858	CARDRGGYGMDVW	1554	hFzd3L, mFzd3L
045S-B05	mFzd3L	GTFSSYPLS	163	GWMNPNSGNTGYA	859	CARGGYNSPLRYW	1555	hFzd3L, mFzd3L
045S-C05	mFzd3L	YTFTSYYMH	164	GIINPSGGSTRYA	860	CARGKDVW	1556	hFzd3L, mFzd3L
045S-D05	mFzd3L	GTFSTHAIS	165	GWMNPNSGNTGYA	861	CAKAGYTAVLDLW	1557	hFzd3L, mFzd3L
045S-E05	mFzd3L	YTFTTYYIH	166	GRMDPNSGKTDSA	862	CARGLSW	1558	hFzd3L, mFzd3L
045S-F05	mFzd3L	NTFTGYYIH	167	GIINPSNGRTSYA	863	CAKDGTGKGVSPLGYW	1559	hFzd3L, mFzd3L
045S-G05	mFzd3L	GTFSSYAIS	168	GWMNPNSGNTGYA	864	CARARGNVGYFDYW	1560	hFzd3L, mFzd3L
045S-A06	mFzd3L	FTFSSYAMH	169	SSISSSSSYIYYA	865	CARGGGYSSSSSEGMDVW	1561	hFzd3L, mFzd3L
045S-B06	mFzd3L	FIFSNYAMH	170	SAIGTGGGTYYA	866	CAREVRHSSSYYYYYGMDVW	1562	hFzd3L, mFzd3L
045S-C06	mFzd3L	FTFSSAWMS	171	SAISGNSVSTYYA	867	CARDLGGYGMDVW	1563	hFzd3L, mFzd3L
045S-D06	mFzd3L	GZFQXVLLS	172	GWMNPNSGNTZYA	868	CAVLAPHVGFDPW	1564	hFzd3L, mFzd3L
045S-E06	mFzd3L	FTFSSYXMS	173	SAISGTGRSTYYA	869	CAKDRYDYAFFDYW	1565	hFzd3L, mFzd3L
045S-G06	mFzd3L	FTFSSYAMH	174	SRINSDGSRTNYA	870	CAGFDYW	1566	hFzd3L, mFzd3L
045S-H06	mFzd3L	FTFSNHYTS	175	SAISGSSGNTYYA	871	CARDGGGYGMDVW	1567	hFzd3L, mFzd3L

045S-A07	mFzd3L	FTFSSYXMS	176	SAISGSGGSTYYA	872	CARDQGGYGMDVW	1568	mFzd3L
045S-C07	mFzd3L	GTFSSYAIS	177	GWMNPNSGNTGYA	873	CARLSSGYDFDYW	1569	hFzd3L, mFzd3L
044S-D01	hFzd3L	GTFSSYAIS	178	GWMSPNSGNTGYA	874	CARFKGIAAAGKYYYYYGMDVW	1570	hFzd3L, mFzd3L
044S-E01	hFzd3L	DTFDTYAIS	179	GGINPSSGSTTYA	875	CARVPPAVAGQPIDYW	1571	hFzd3L, mFzd3L
044S-F01	hFzd3L	GTFSSYAIS	180	GWMNPNSGNTGYA	876	CANLGYSSGTYYFDYW	1572	hFzd3L, mFzd3L
044S-G01	hFzd3L	YTFTNYFMH	181	GIINPSGGSTSYA	877	CARDDGGGMDVW	1573	hFzd3L, mFzd3L
044S-A02	hFzd3L	GTFSSYAIS	182	GWMNPNSGNTGYA	878	CARAKYYYDMDVW	1574	hFzd3L, mFzd3L
044S-B02	hFzd3L	FNFRMRPMH	183	SYISGNSGYTNYA	879	CARGPNWFDPW	1575	hFzd3L, mFzd3L
044S-C02	hFzd3L	YTFTAYYMH	184	GIINPSGGSTSYA	880	CARDRTGRWDVW	1576	hFzd3L, mFzd3L
044S-D02	hFzd3L	YTFTNYYMH	185	GRMNPNSGNTVYA	881	CASRGGDGMDVW	1577	hFzd3L, mFzd3L
044S-E02	hFzd3L	FTVSDKYMS	186	AVISYDGSNKYYA	882	CAREGYSSSWYSPEYFQHW	1578	hFzd3L, mFzd3L
044S-F02	hFzd3L	FPFSSYAMS	187	SFISGSGGSTDYA	883	CARAVRGVTPLGYW	1579	hFzd3L, mFzd3L
044S-H02	hFzd3L	FTFSSYAMH	188	AVISYDGSNKYYA	884	CARSTRGVGLDYW	1580	hFzd3L, hFzd6L
044S-B03	hFzd3L	YTFTGYYMH	189	GRINPANGNASYA	885	CARGSRHC	1581	hFzd3L, hFzd6L
044S-C03	hFzd3L	YTFTGYYMH	190	GRINPDSGYTNYA	886	CAHLKDDYW	1582	hFzd3L, hFzd6L
044S-D03	hFzd3L	FTFSNHYMS	191	SAIGTGGGTYYA	887	CARGGRYQGNW	1583	hFzd3L, mFzd3L
044S-E03	hFzd3L	YTFTSYYMH	192	GIINPRRGSTRYA	888	CARDGVDRFDYW	1584	hFzd3L, mFzd3L
044S-F03	hFzd3L	FTFSNYAMH	193	SAISGSGGSTYYA	889	CAREEYGMDVW	1585	hFzd3L, hFzd6L
044S-G03	hFzd3L	FTFNNYAMS	194	TVISSDGSTKSYA	890	CARALEWPNSGYFDYW	1586	hFzd3L, mFzd3L
044S-A04	hFzd3L	YTFTRYAMH	195	GWMNPNSGNTGYA	891	CARDLIFRGSGYGMDVW	1587	hFzd3L, mFzd3L
044S-C04	hFzd3L	YIFTNHYIH	196	GWMNPSSGNTGYA	892	CAIQDVW	1588	hFzd3L, hFzd6L
044S-D04	hFzd3L	GTFSSYAIN	197	GWINPNSGNTGYA	893	CARGPYSRTVPYYYGMDVW	1589	hFzd3L, hFzd6L
044S-A01	hFzd3L	YTFTSYGIS	198	GGIIPMSGTSNYA	894	CARGKHYW	1590	hFzd3L
044S-B01	hFzd3L	YTFTGYYVH	199	GWINPKNGGTHYA	895	CARSGSERLSGYSPR	1591	mFzd3L
044S-C01	hFzd3L	FTFSSSWMH	200	ASISSSSSHIYYA	896	CARLTTSTVTTQYWYFDLW	1592	mFzd3L
044S-G02	hFzd3L	FTFNNYZMS	201	TVISSDGSTZSYA	897	CARALEWPNSGYFDYW	1593	hFzd3L, mFzd3L
044S-H03	hFzd3L	FSFINYAMH	202	SSISSSSSYIYYA	898	CARGLYGAFQYW	1594	mFzd3L
044S-B04	hFzd3L	FTFNNYAMS	203	SAISGSGGSTYYA	899	CARGIGYMDVW	1595	mFzd3L
044S-G04	hFzd3L	YTFVRYGIT	204	GWINPNSGGTNYA	900	CARINGTIVASYYYYGMDVW	1596	mFzd3L
044S-H04	hFzd3L	DTFSNYYMH	205	GLITPSGDYATYA	901	CASHRHW	1597	hFzd3L, mFzd3L
044S-A05	hFzd3L	YTFTDYSLH	206	GGIIPVLGTTKYA	902	CAHVPPTGAAGAFDIW	1598	hFzd3L, mFzd3L
044S-B05	hFzd3L	YTFSSYYMH	207	GIINPNGGGTRYA	903	CARHNYDSYYYYGMDVW	1599	mFzd3L
044S-C05	hFzd3L	GTFSSYAIS	208	GWMNPNSGNTGFA	904	CARLGLEWEFDYW	1600	hFzd3L, mFzd3L
044S-D05	hFzd3L	GTFSSYAIS	209	GKINPRDGSTTYA	905	CARGSGGGW	1601	hFzd3L, hFzd6L

044S-E05	hFzd3L	FTFSSYXMS	210	STISGNGGRTYYA	906	CARTGDGMDVW	1602	hFzd3L, mFzd3L
044S-G05	hFzd3L	YTFTSYSMH	211	GWMNPNTGNTGYA	907	CATVPSGSYWVDYW	1603	hFzd3L, hFzd6L
044S-H05	hFzd3L	FTFSSYXMS	212	SAISGSGGSTYYA	908	CARDTGGTFNYW	1604	hFzd3L, mFzd3L
044S-A06	hFzd3L	FSLSSSGMS	213	SAISRSGATTYYS	909	CARPRVEAFDIW	1605	hFzd3L, mFzd3L
044S-B06	hFzd3L	YTFSNYYMH	214	GWINPKSGGTNYA	910	CARDYSNYAFASYYYYMDVW	1606	hFzd3L, mFzd3L
044S-C06	hFzd3L	GTFSRYAIS	215	GWMNPNSGNTGYA	911	CARMAYSYGYDWFDPW	1607	hFzd3L, mFzd3L
044S-D06	hFzd3L	YTFTNYFFH	216	GWMNPHSGNTGYA	912	CAREYYYYGMDVW	1608	hFzd3L, mFzd3L
044S-E06	hFzd3L	YTFTSYYMH	217	GMINPSGQSTTYA	913	CARGGVW	1609	hFzd3L, mFzd3L
044S-F06	hFzd3L	YTFTTHYMH	218	GIINPSGGTTNYA	914	CARDRYCSGGSCTGLFDYW	1610	hFzd3L, mFzd3L
044S-G06	hFzd3L	YTFSHHYVH	219	GWISAYNGKTNYA	915	CAREGGGMDVW	1611	hFzd3L, mFzd3L
044S-H06	hFzd3L	YSFTNYYLH	220	GWMNPNSGNTGYA	916	CARDPYGSGTGGMDVW	1612	hFzd3L, mFzd3L
044S-A07	hFzd3L	YTFSHYGMH	221	AAVSRSGGSTFYA	917	CARGGMDVW	1613	hFzd3L, mFzd3L
044S-B07	hFzd3L	GTFSSYAIS	222	GVINPSGGSTSYA	918	CASRVSRSW	1614	hFzd3L, mFzd3L
044S-C07	hFzd3L	FTFSSFAMH	223	SGINWNGGSTGYA	919	CARDHPPRSSSRYFGLW	1615	hFzd3L, mFzd3L
044S-D07	hFzd3L	YDFINYYIH	224	GWISGYNGNTNYA	920	CAREKQGMDVW	1616	hFzd3L, mFzd3L
044S-E07	hFzd3L	YTFTYRYLH	225	GIINPDTGSATYA	921	CARGTGSGSSW	1617	hFzd3L, mFzd3L
044S-F07	hFzd3L	YTFTSYYMH	226	GWMNPNSGNTGYV	922	CARALSRGNYW	1618	hFzd3L, mFzd3L
044S-G07	hFzd3L	FTFTSSAVQ	227	GWISAYSGNTNYA	923	CARVGVGGYSYGLPYYYMDVW	1619	mFzd3L
044S-H07	hFzd3L	YTFTTHYMH	228	GMINPSGGSTSYA	924	CARGKTNW	1620	hFzd3L, mFzd3L
044S-A08	hFzd3L	FTFGSHGMH	229	SGISSNGGSTYYA	925	CARGGRRSSGWYGVDYW	1621	hFzd3L, mFzd3L
044S-B08	hFzd3L	GSFTSHAVT	230	GWMNPNSGNTGYA	926	CARVLIYGMDVW	1622	mFzd3L
044S-C08	hFzd3L	GTFSRNAIS	231	GWMNPNSGNTGYA	927	CARDTGGYMDVW	1623	hFzd3L, mFzd3L
044S-E08	hFzd3L	YTFTDNYIH	232	GMINPSGGSTSYA	928	CARKGDYW	1624	hFzd3L, mFzd3L
044S-F08	hFzd3L	GRFSTYALS	233	GWMNPNSGNTGYA	929	CARIGYYYMDVW	1625	hFzd3L, mFzd3L
044S-G08	hFzd3L	FTYDDHAMH	234	SAISGGGGSTYYA	930	CARGDLRWRGWYFDLW	1626	hFzd3L, mFzd3L
044S-A09	hFzd3L	YTFTSYYMH	235	GLINPSGGSTRYA	931	CARDYGDIGFDYW	1627	hFzd3L, mFzd3L
044S-B09	hFzd3L	YPFSNYYMH	236	GIINSRRGSTRYA	932	CARDHGDAFDIW	1628	hFzd3L, mFzd3L
044S-C09	hFzd3L	YTFTTYWIH	237	GVINPSGGSTSYA	933	CARDSGRYRGRYFDYW	1629	hFzd3L, mFzd3L
044S-E09	hFzd3L	FPFSSYGIH	238	SAISASGGGTYYA	934	CASGAAAFDIW	1630	hFzd3L, mFzd3L
044S-F09	hFzd3L	YTFTYRYLH	239	GRINTNSGDTNYA	935	CAREEHW	1631	hFzd3L, hFzd6L
044S-G09	hFzd3L	FTFSSDAMH	240	SAISGTTGRTYYA	936	CARDRYSSSWAHLYFDLW	1632	hFzd3L, mFzd3L
044S-H09	hFzd3L	FTFSTYPMH	241	AAIWNDGTNKYYA	937	CARVAARPQRALGYW	1633	hFzd3L, hFzd6L
044S-A10	hFzd3L	YTFNSYYMH	242	GTINPRRGSTKYA	938	CARVANWAVDYW	1634	hFzd3L, mFzd3L
044S-B10	hFzd3L	GTFSSYAIS	243	GWINPNSGNRGYA	939	CARHRYSSSWNYGMDVW	1635	hFzd3L, mFzd3L

044S-D10	hFzd3L	YTFTSYYMH	244	GMINPRGGGTGYA	940	CARTSKDVGLFDYW	1636	hFzd3L, mFzd3L
038S-B01	hFzd4L	YTFTSYYMH	245	GWMNPSGGNTGYA	941	CARDGSLDLW	1637	hFzd4L
038S-D01	hFzd4L	YTFTGYYMH	246	GVINPSGGSTIYA	942	CAKVYKYYDYVWGSLDYW	1638	hFzd4L
038S-D03	hFzd4L	YTFTSYYMH	247	GRIIPNTGDTNYA	943	CATLPRGRGNYW	1639	hFzd4L
038S-E02	hFzd4L	YTFTGYYVH	248	GIINPSGGTTSYA	944	CAREGRYCSGGSCYSGWYFDLW	1640	hFzd4L
038S-E03	hFzd4L	YTFTNYYMH	249	GWMQGDSGNTGYA	945	CARDGSLDYW	1641	hFzd4L
038S-E05	hFzd4L	YTFTNYYMH	250	GWMNPNSGNTGYA	946	CARDASFDYW	1642	hFzd4L
038S-A04	hFzd4L	YTFTGYYMH	251	GWMNPNSGNTGYA	947	CARDGSMDVW	1643	hFzd4L
038S-D04	hFzd4L	YTFSSYYMH	252	GWZNPNGGNTZYA	948	CARDGSLDYW	1644	hFzd4L
038S-E01	hFzd4L	YTFTGYYMH	253	GWINPNSGNTGYA	949	CARGGNRDYR	1645	hFzd4L
038S-C08	hFzd4L	YTFTGYYMH	254	GWMNPNSGNTAYA	950	CAREGRYCSGGSCYSGWYFDLW	1646	hFzd4L
038S-A03	hFzd4L	YTFTGYYMH	255	GWINPNSGGTNYA	951	CAREARRGGWSTGYFDLW	1647	hFzd4L
039S-B03	hFzd4L	YTFTGYYMH	256	GWINPYSGGTSYA	952	CAREARRGGWSTGYFDLW	1648	hFzd4L
038S-B02	hFzd4L	FTFSNHYMS	257	SSISSSSSYIYYA	953	CARGPRTYSSSGFDYW	1649	hFzd4L
038S-G03	hFzd4L	YTFTSYYMH	258	GRIIPNTGDTSYA	954	CATLPRGKGNYW	1650	hFzd4L
039S-B06	hFzd4L	FTFSNHYMS	259	SSISSGSGYIYYA	955	CAKGPSSGWYVFDYW	1651	hFzd4L
038S-C02	hFzd4L	FTFSSYXMS	260	SAISGSGGSTYYA	956	CARDRGRWYGENWFDPW	1652	hFzd4L
039S-B02	hFzd4L	YTFTSYYMH	261	GWMNPNSGNTGYA	957	CARDYGGYDYW	1653	hFzd4L
038S-B04	hFzd4L	YTFTSYYMH	262	GWINPNSGGTNYA	958	CARGRGGGYRGGYW	1654	hFzd4L
039S-G02	hFzd4L	FTFSNHYTS	263	ASISSSSSYIYYA	959	CARDVMVRGVDYYGMDVW	1655	hFzd4L
039S-F04	hFzd4L	YTFTSYYMH	264	GWMNPNSGNTGYA	960	CARDGSMDVW	1656	hFzd4L
038S-B08	hFzd4L	YTFTGYYMH	265	GWMNPNSGNTGYA	961	CARDGSMDVW	1657	hFzd4L
038S-C10	hFzd4L	YTFTNYYMH	266	GVINPSGGSTVYA	962	CARHDRHDYGDLDYW	1658	hFzd4L
038S-F06	hFzd4L	FTFSSYAMH	267	SGITGSGGATYYA	963	CARDGDYVSGYGMDVW	1659	hFzd4L
038S-F07	hFzd4L	FTFSSYGMH	268	SAISGSGGSTYYA	964	CARRLQAVHWFDPW	1660	hFzd4L
038S-H06	hFzd4L	YTFTSYYMH	269	GWMNPNSGNTGYA	965	CARDGSMDVW	1661	hFzd4L
038S-G07	hFzd4L	FTFSSYGMH	270	SAISGSGGSTYYA	966	CARRLQAVHWFDPW	1662	hFzd4L
038S-F12	hFzd4L	YTFTSYYMH	271	GWINTKTGAANYA	967	CARDSSLDYW	1663	hFzd4L
038S-B07	hFzd4L	YTFTGYYVH	272	GRINPNSGATNYA	968	CATGVVTANTYDYW	1664	hFzd4L
039S-B04	hFzd4L	FTFSNHYMS	273	SSISGRSSFIYYA	969	CARVHGGNSLFYFQHW	1665	hFzd4L
039S-C02	hFzd4L	FTFSNHYMS	274	SAVDGAGTNTYYA	970	CARGGGSYW	1666	hFzd4L
039S-H05	hFzd4L	YTFTNYYMH	275	GWMNPSNGDTGYA	971	CARDGSLDLW	1667	hFzd4L
039S-G01	hFzd4L	YTFTAYYMH	276	GVINPSGGRTTYA	972	CARSSGGYSYGQIDYW	1668	hFzd4L
039S-E03	hFzd4L	YTFTSYYMH	277	GWMNPNSGDTGYA	973	CARDGSLDYW	1669	hFzd4L

039S-C01	hFzd4L	YTFTGYYMH	278	GWMNPNSGNTGYA	974	CARDGSGDYW	1670	hFzd4L
039S-F02	hFzd4L	YTFTGYYMH	279	GVINPSGGSTTYA	975	CARGYWGGYFDLW	1671	hFzd4L
039S-E04	hFzd4L	YTFTGYYMH	280	GWMNPNSGNTGYA	976	CARDGSMDVW	1672	hFzd4L
039S-C05	hFzd4L	YTFTSYGIS	281	GWINPKSGGTRYA	977	CARGPSQNYYGMDVW	1673	hFzd4L
039S-F06	hFzd4L	FTFSNHYMS	282	SAISGTGRYTYYA	978	CARDRRYSSGQNYYYYYMDVW	1674	hFzd4L
039S-A07	hFzd4L	YTFTSYYMH	283	GWINPNSGGAHYA	979	CARGGNWFDPW	1675	hFzd4L
039S-E10	hFzd4L	YTFTSYYMH	284	GWMNPNSGNTGYA	980	CARDGSFDYW	1676	hFzd4L
039S-G07	hFzd4L	FTFSSYGMH	285	SGISGSGGRTYYA	981	CARRHPIGAFDIW	1677	hFzd4L
039S-A10	hFzd4L	YTFTNYYMH	286	GWMNPKSGNTGYA	982	CARDGALDYW	1678	hFzd4L
039S-B07	hFzd4L	YTFTGYYMH	287	GWMNPNSANTGYA	983	CARDGSLDYW	1679	hFzd4L
039S-B09	hFzd4L	YTFTTYYMH	288	GWMNPNTGNTGYA	984	CARDGAMDVW	1680	hFzd4L
039S-A08	hFzd4L	YTFTSYYMH	289	GRIIPNTGDTNYA	985	CATLPRGRGNYW	1681	hFzd4L
039S-C09	hFzd4L	YTFTGYYMH	290	GWINPNSGNTGYA	986	CARDGSLDLW	1682	hFzd4L
039S-E07	hFzd4L	YTFTGYYMH	291	GVIIPSGGSTLYA	987	CARGGYSNYGMDVW	1683	hFzd4L
039S-H09	hFzd4L	YTFTSYYMH	292	GVINPSGGATRFA	988	CARDGSMDVW	1684	hFzd4L
040S-B01	hFzd4L	YTFTGYYMH	293	GWMNPHNGDTGYA	989	CARDGSFDYW	1685	hFzd4L
040S-A02	hFzd4L	FTFSSYAMH	294	SGIRGSGGATYYA	990	CARDGDYVSGYGMDVW	1686	hFzd4L
040S-H04	hFzd4L	FTFSSYAMH	295	AVISYDGSNKYYA	991	CAKIGTW	1687	hFzd4L
040S-E05	hFzd4L	YTFTGYYMH	296	GWINSNSGGTNYA	992	CARDGSLDFW	1688	hFzd4L
039S-H10	hFzd4L	YTFTTYYIH	297	GWMNPNTGYTGYA	993	CARDGSLDYW	1689	hFzd4L
040S-B02	hFzd4L	YTFTGYYVH	298	GRINPNSGATNYA	994	CATGVVTANTYDYW	1690	hFzd4L
040S-C02	hFzd4L	YTFTNYYMH	299	GWMNPNSGNTGYA	995	CARDGALDYW	1691	hFzd4L
040S-A05	hFzd4L	YTFTGYYVH	300	GWVZAFNGDTNYA	996	CARDGSMDVW	1692	hFzd4L
039S-C12	hFzd4L	YTFTGYYMH	301	GWMNPNSGNTGYA	997	CARDGSMDVW	1693	hFzd4L
039S-F12	hFzd4L	YTFTSYYMH	302	GRIIPNTGDTNYA	998	CATLPRGRGNYW	1694	hFzd4L
040S-E01	hFzd4L	YTFTSYYMH	303	GWMNPNSGNTGYA	999	CARDGSFDYW	1695	hFzd4L
040S-E02	hFzd4L	YTFTSYYMH	304	GWMNPSSGNTGYA	1000	CARDGSLDLW	1696	hFzd4L
039S-F11	hFzd4L	YTFTSYYMH	305	GWMNPNSGNTGYA	1001	CARDGSMDVW	1697	hFzd4L
040S-F01	hFzd4L	YTFTGYYMH	306	GWMNPHSANTGFA	1002	CARDGSMDVW	1698	hFzd4L
040S-F02	hFzd4L	YTFTGYYMH	307	GWINPNSGNTGFA	1003	CAREGRHDFWSGYFFDYW	1699	hFzd4L
040S-E04	hFzd4L	YTFTGYYVH	308	GWVSAFNGDTNYA	1004	CARDGSMDVW	1700	hFzd4L
040S-D05	hFzd4L	GTFSSYAIS	309	GRIIPILGIANYA	1005	CARAVGSSSSNYYYYYGMDVW	1701	hFzd4L
039S-G11	hFzd4L	YTFTGYYMH	310	GMIIPRHGGTAYA	1006	CARVPRGGENYW	1702	hFzd4L
040S-G01	hFzd4L	FTFSSYAMH	311	AVISYDGSNKYXA	1007	CARGRKRSSGWHFDYW	1703	hFzd4L

036S-C01	hFzd5L	YTFTGHYIH	312	GIINZSSGSTTYA	1008	CAREGYSYYGMDVW	1704	hFzd5L
036S-F01	hFzd5L	FTFSNHYTS	313	STIGTGGGTYYA	1009	CGKSYPYYYHCIDVW	1705	hFzd5L, mFzd5L
036S-B02	hFzd5L	YTFSAYYMN	314	GIIDAGGRTSNA	1010	CARDLGYGFDYW	1706	hFzd5L
036S-D02	hFzd5L	FSVSSNYMT	315	SSIGVNGDTYYL	1011	CARHKDGGDMGYW	1707	hFzd5L
036S-F02	hFzd5L	GTFSSYAIS	316	GIINPSGGSTZYA	1012	CASYDYYYYYGMDVW	1708	hFzd5L
036S-G02	hFzd5L	GTFZZYZIZ	317	EZINPSGGSTSYA	1013	CASYDYYYYYGMDVW	1709	hFzd5L
036S-H02	hFzd5L	FTFSNHYTS	318	STIGTGGGTYYA	1014	CAKSDPYYYHGIDVW	1710	hFzd5L
036S-A03	hFzd5L	FSVSSNYMT	319	SSIGVNGDTYYL	1015	CARHKDGGDMGYW	1711	hFzd5L
036S-C03	hFzd5L	YTFASYDIN	320	GIINPSGGSTSYA	1016	CARYSSSVYYGMDVW	1712	hFzd5L
036S-C04	hFzd5L	YTFTGYYMH	321	GIINPRDGDTVYA	1017	CARDGVAAAAAYYMDVW	1713	hFzd5L
036S-D04	hFzd5L	YTFTGHYIH	322	GIINPSSGSTTYA	1018	CAREGYSYYGMDVW	1714	hFzd5L
036S-E04	hFzd5L	GTFSSYAIS	323	GIINPSGGSTSYA	1019	CASYDYYYYYGMDVW	1715	hFzd5L
036S-A05	hFzd5L	YTFTSYFMH	324	GIINZSGGSTSYA	1020	CARDYGDYELGDNYYYYGMDVW	1716	hFzd5L, mFzd5L
036S-B05	hFzd5L	YTFTSYYMH	325	GIINPSGGSTSYA	1021	CARSIAGMDVW	1717	hFzd5L
036S-C05	hFzd5L	FSVSSZYMT	326	SSIGVNGDTYYL	1022	CARHKDGGDMGYW	1718	hFzd5L
036S-D05	hFzd5L	GTFSSYAVS	327	GWIIPFSGTVNYA	1023	CARFDGYYYYGMDVW	1719	hFzd5L
036S-D01-3	hFzd5L	FTFSSYAMS	328	SSISSSGSYIDYA	1024	CAKDRFAKDYGYFQHW	1720	hFzd5L
036S-D02-5	hFzd5L	FTFDDYAMH	329	SGINWNGGSTGYA	1025	CARDSRSGDYFDYW	1721	hFzd5L
036S-G03-3	hFzd5L	GTFSSYAIS	330	GWINPNNGGTDYA	1026	CARDIVWFGGYYYYGMDVW	1722	hFzd5L
040S-D07	hFzd6L	YTFTSYYMH	331	GWINPNSGGTNYA	1027	CARDSGHW	1723	hFzd6L, mFzd6L
040S-E08	hFzd6L	YTFTSYYIH	332	GWINPSSGDTKYA	1028	CAKTGVW	1724	hFzd6L, mFzd6L
040S-B09	hFzd6L	FSFTSHGMH	333	SAISGSGGSTYYA	1029	CARGVSRRAFDIW	1725	hFzd6L, mFzd6L
040S-H09	hFzd6L	YIFTGYYMH	334	GIIDPSGGSTSYA	1030	CARRGFDPW	1726	hFzd6L, mFzd6L
040S-E10	hFzd6L	GTFSGYAIS	335	GWMNPSRGNTVYA	1031	CARQGVGAKYGMDVW	1727	hFzd6L, mFzd6L
040S-D11	hFzd6L	GTFSDYYIH	336	GMINPIFGTAKYA	1032	CARSTNW	1728	hFzd6L, mFzd6L
041S-B01	hFzd6L	FTFSSYAMH	337	SSISSSSSYIYYA	1033	CARTGTTYRSFDYW	1729	hFzd6L, mFzd6L
040S-E07	hFzd6L	FTFRTHAMH	338	AVISKDGSQRYYA	1034	CASSSSSLRSHDYW	1730	hFzd6L, mFzd6L
040S-B08	hFzd6L	YTFTTYSIH	339	GWMNPNTGNTGYA	1035	CARLPGGAVAGFDYW	1731	hFzd6L, mFzd6L
040S-F08	hFzd6L	YTFTGYYMH	340	GIINPSAGSTNYA	1036	CARDAVSRGRFDYW	1732	hFzd6L, mFzd6L
040S-B12	hFzd6L	YTFTGYSLH	341	GRINPNSGGTDYA	1037	CATRMDVW	1733	hFzd6L, mFzd6L
040S-H06	hFzd6L	YTFSNYYIH	342	GIINPSGGSTSYA	1038	CARTDALSVVRGVPFDYW	1734	hFzd6L, mFzd6L
040S-F07	hFzd6L	FTFSDYYMS	343	SHIKSDGSSTRYA	1039	CARVKVPAAGLNYWFDPW	1735	hFzd6L, mFzd6L
040S-G08	hFzd6L	GTFSSYAIS	344	GIINPSGGSTSYA	1040	CARSDYYYYYMDVW	1736	hFzd6L, mFzd6L
040S-B10	hFzd6L	GTFSNYAYS	345	GWMNPSSGNTGYA	1041	CARWTRDSSGYIDYW	1737	hFzd6L, mFzd6L

040S-G10	hFzd6L	DTFTRHYVH	346	GRINPNSGGTNYA	1042	CASQDIW	1738	hFzd6L, mFzd6L
040S-C12	hFzd6L	YTFTNYYMH	347	GWINPNSGGTKFA	1043	CARDKGNW	1739	hFzd6L, mFzd6L
040S-A07	hFzd6L	YTFASYYIH	348	GWISAYNGNTQHA	1044	CARGRKAFDIW	1740	hFzd6L, mFzd6L
040S-G07	hFzd6L	FTFSSYAMH	349	SAISGTGDNTYYA	1045	CARSAAGTRAFDYW	1741	hFzd6L, mFzd6L
040S-C10	hFzd6L	YTFNNYYMH	350	AIINPNGGATSYA	1046	CARDSGDYYFDYW	1742	hFzd6L, mFzd6L
040S-F12	hFzd6L	YTFTGYYMH	351	GRMNPNSGNTVYA	1047	CARGGYGDEGPW	1743	hFzd6L, mFzd6L
040S-E11	hFzd6L	FTFGDYAMS	352	TGISYDASKEYYA	1048	CAKYSSSWYYFDYW	1744	hFzd6L, mFzd6L
040S-G12	hFzd6L	YTFTGYYMH	353	GIINPTSGKTSYA	1049	CARRGFDYW	1745	hFzd6L, mFzd6L
041S-D01	hFzd6L	HTFSSYVLG	354	GWINPNSGGTNYA	1050	CARGTRRMFDYW	1746	hFzd6L, mFzd6L
040S-H07	hFzd6L	YTLTTYYMH	355	GIIDPNSGRTSYA	1051	CARNNYYDSSGPKGIDYW	1747	hFzd6L, mFzd6L
040S-C08	hFzd6L	FTFSSYAMH	356	SAISTSGDSTYYA	1052	CARSLIRRYFDLW	1748	hFzd6L, mFzd6L
040S-H08	hFzd6L	FTFSSYAMH	357	SAISGSGGSTYYA	1053	CASSSSLVRAFDIW	1749	hFzd6L, mFzd6L
040S-C09	hFzd6L	YTFTGNYMH	358	GWMNPSSGNTGYA	1054	CARVGRDYYYGMDVW	1750	hFzd6L, mFzd6L
040S-H10	hFzd6L	YTFTRYYMH	359	GWMDPYSGNTGYA	1055	CARPGYSSGWAFDYW	1751	hFzd6L, mFzd6L
040S-F11	hFzd6L	YTFTNYYVH	360	GWMNPNSGNTGYA	1056	CAKGIAAAGTWSGYYGMDVW	1752	hFzd6L, mFzd6L
041S-A01	hFzd6L	YTFTNHGIS	361	GGINPNSGGTNYA	1057	CARHQRAAAGRKGFDYW	1753	hFzd6L, mFzd6L
041S-E01	hFzd6L	GAFSSYAIS	362	GIINPNSGDTGYA	1058	CARHALSSTGYMDVW	1754	hFzd6L, mFzd6L
040S-B07	hFzd6L	YTFTRYYLH	363	GIINPSGGSTTYA	1059	CARGGRYAFDIW	1755	hFzd6L, mFzd6L
040S-D08	hFzd6L	FTVSRNYMD	364	ATISGTGGSIYYA	1060	CARPRTVTRRGWYFDLW	1756	hFzd6L, mFzd6L
040S-D09	hFzd6L	YTFTSYYMH	365	GWISADNGNTNYA	1061	CARDRYYW	1757	hFzd6L, mFzd6L
040S-F09	hFzd6L	FAFSSYALH	366	SVISGSGGTTYYA	1062	CAREFRATGKSMDVW	1758	hFzd6L, mFzd6L
040S-D10	hFzd6L	YSFSSYYMH	367	GWINPNSGGTNYA	1063	CARDKTAW	1759	hFzd6L, mFzd6L
040S-A11	hFzd6L	YTFTSYYMH	368	GGTIPIYGTTNYA	1064	CARGRNYGDYDDYW	1760	hFzd6L, mFzd6L
040S-D12	hFzd6L	FTFHNSAMH	369	SAIGTGGGTYYA	1065	CTTRPWGSDYW	1761	hFzd6L, mFzd6L
041S-F01	hFzd6L	FTFSSHGMH	370	SAMNFNTGSTYYA	1066	CANDRLGYW	1762	hFzd6L, mFzd6L
040S-B11	hFzd6L	YTFTSYDIN	371	GMINPDVGSTSYA	1067	CARGQWLAYGMDVW	1763	hFzd6L, mFzd6L
040S-G11	hFzd6L	FTFSSYAMS	372	SAISGSGGSTYYA	1068	CARHYRYSGGGAFDIW	1764	hFzd6L, mFzd6L
040S-C07	hFzd6L	GTFSSYAIS	373	GIINPSGGRTSYA	1069	CASSDKIRSLDVW	1765	hFzd6L, mFzd6L
040S-A08	hFzd6L	YTFTGYYVH	374	GWISAYNGNTNYA	1070	CARVSPYSGWGFDYW	1766	hFzd6L, mFzd6L
040S-A09	hFzd6L	DTFTSYYMH	375	GWMNPNSGNTGYA	1071	CARYSGSYPQNWYFDLW	1767	hFzd6L, mFzd6L
040S-C11	hFzd6L	GTFSGYAIS	376	GWINPNSGGTNYA	1072	CARAGRYYYYGMDVW	1768	hFzd6L, mFzd6L
040S-H11	hFzd6L	YTFTNYYMH	377	GWINPKSGGTHFA	1073	CARTQFAGYFDLW	1769	hFzd6L, mFzd6L
041S-D02	hFzd6L	YTFTSNYIH	378	GRITPSDGTTTYA	1074	CARGGYGDSGYW	1770	hFzd6L, mFzd6L
041S-A04	hFzd6L	FTFSGYYMH	379	GIINPSGGSTSYA	1075	CARGDRYYYYMDVW	1771	hFzd6L, mFzd6L

041S-A08	hFzd6L	FTFSSSAMH	380	SAIGIGGGTYYA	1076	CAKSTDYSKAFDYW	1772	hFzd6L, mFzd6L
041S-F08	hFzd6L	YTFTSYYMH	381	GWMNPNSGNTGYA	1077	CARGRYAFDVW	1773	hFzd6L, mFzd6L
041S-H01	hFzd6L	FTFSSYAMH	382	SAISGSAAGTYYA	1078	CARSGPGYRAFDIW	1774	hFzd6L, mFzd6L
041S-E02	hFzd6L	YTFTDYYMH	383	GIINPSGGSTSYA	1079	CARDGGDYYFDYW	1775	hFzd6L, mFzd6L
041S-C03	hFzd6L	FTFSSHSTH	384	SGLSASGANTYYA	1080	CARSTPRVFDLW	1776	hFzd6L, mFzd6L
041S-F06	hFzd6L	GTFSNQAIS	385	GWMNPHSGNTGLA	1081	CARVTPYCGGDCYSDDYW	1777	hFzd6L, mFzd6L
041S-F07	hFzd6L	YTFZAZHMH	386	GIINPSGGSTSYA	1082	CARRGFDYW	1778	hFzd6L, mFzd6L
041S-G08	hFzd6L	FSFSSYGMT	387	SAIGTGGGTYYA	1083	CARAARSRYYMDVW	1779	hFzd6L, mFzd6L
041S-F02	hFzd6L	FTFSSYAMH	388	AVISKDESNKYYA	1084	CAKSSSSRRAFDYW	1780	hFzd6L, mFzd6L
041S-D03	hFzd6L	YTFTGYYMH	389	GWMNPNSGNTGYA	1085	CARVYRGSYYGMDVW	1781	hFzd6L, mFzd6L
041S-C05	hFzd6L	YTFTSYYVH	390	GIINPSGGATSYA	1086	CARTDYYYYYMDVW	1782	hFzd6L, mFzd6L
041S-G06	hFzd6L	YTFTSYYMH	391	GIIDPNSGRTGYA	1087	CARDSRLAREFDYW	1783	hFzd6L, mFzd6L
041S-C08	hFzd6L	YTFTNYYIH	392	GWINPNSGGTNYA	1088	CASGGRHW	1784	hFzd6L, mFzd6L
041S-H08	hFzd6L	YTFNNYYMH	393	AIINPNGGATSYA	1089	CARDSGDYYFDYW	1785	hFzd6L, mFzd6L
041S-E09	hFzd6L	FTFSSYAMH	394	STISXNSRSIDYA	1090	CARTYPAIRAFDIW	1786	hFzd6L, mFzd6L
041S-G02	hFzd6L	YTFTGYYMH	395	GRINPSGGRTTYA	1091	CARGGPSGDYW	1787	hFzd6L, mFzd6L
041S-C04	hFzd6L	DSFTNYYMH	396	GRINPNSGGTNYA	1092	CARGGADFDYW	1788	hFzd6L, mFzd6L
041S-D05	hFzd6L	YTFASYYVH	397	GRINPINGGTNYA	1093	CARGSYYGDYGPW	1789	hFzd6L, mFzd6L
041S-A06	hFzd6L	YTFTSYGIS	398	GWINPNSGGTNYA	1094	CARFYDAFDIW	1790	hFzd6L, mFzd6L
041S-H06	hFzd6L	FTFSSYAMH	399	SAISGSGGSTYYA	1095	CARSTIWGRAFDIW	1791	hFzd6L, mFzd6L
041S-F09	hFzd6L	YTFTSYYMH	400	GIINPSGGSTSYA	1096	CARDGQGAGGYYYYGMDVW	1792	hFzd6L, mFzd6L
041S-B02	hFzd6L	YTFTSYYMH	401	GIINPSGGSTTYA	1097	CARGGRIW	1793	hFzd6L, mFzd6L
041S-H02	hFzd6L	FIFSSYAMS	402	SGISGSSASTYYA	1098	CARGRRAARTFDYW	1794	hFzd6L, mFzd6L
041S-F03	hFzd6L	FRFSNYAMT	403	SGVDGSGGKTYYA	1099	CAKVLRSGRNFDYW	1795	hFzd6L, mFzd6L
041S-D04	hFzd6L	YTFTGYYLH	404	GWMSPKNGDTRFA	1100	CARVGYGMDVW	1796	hFzd6L, mFzd6L
041S-G04	hFzd6L	FTFSSYAMH	405	SAISGSGGSTYYA	1101	CARVGSGWSRAFDYW	1797	hFzd6L, mFzd6L
041S-E05	hFzd6L	YTFTGYYMH	406	GIINPSGGSTSYA	1102	CARDNQDYYFDYW	1798	hFzd6L, mFzd6L
041S-A07	hFzd6L	LSVGSNYMS	407	SAISFGGSTYYA	1103	CARDRVEQLDGAKRYYYYGMDVW	1799	hFzd6L, mFzd6L
041S-H07	hFzd6L	FTFSTYAMH	408	SAISASGGRTYYA	1104	CAKALRGGLDYW	1800	hFzd6L, mFzd6L
041S-D08	hFzd6L	FAFSGSAMH	409	SGISGSGGSTFYA	1105	CARTRVAYFDYW	1801	hFzd6L, mFzd6L
041S-A09	hFzd6L	YTFTRHYVH	410	GVINPSGGSANYA	1106	CARDLRKAGTRWFDPW	1802	hFzd6L, mFzd6L
041S-G03	hFzd6L	FTFSGSALH	411	SAISGSGGSTYYA	1107	CALRGVW	1803	hFzd6L, mFzd6L
041S-E04	hFzd6L	NTFIGYNMH	412	GGIIPLFGTTNYA	1108	CAKEATGTGAFQHW	1804	hFzd6L, mFzd6L
041S-H04	hFzd6L	YTFTNYYIH	413	GWMNPNSGNTGYA	1109	CARSGSSRYYYGMDVW	1805	hFzd6L, mFzd6L

041S-F05	hFzd6L	FTFSSYAMH	414	SAIGAGGGTYYA	1110	CANSLPAPHAFDIW	1806	hFzd6L, mFzd6L
041S-C06	hFzd6L	YTFTRHYVH	415	GIINPSGGSATYA	1111	CARDSGTRRWHGMDVW	1807	hFzd6L, mFzd6L
041S-B07	hFzd6L	YTFTSYGIS	416	GWINPNSGDTKYS	1112	CARGLGGETW	1808	hFzd6L, mFzd6L
041S-B09	hFzd6L	YAFTGYYMH	417	GWINPNNGGTNYA	1113	CARDRNYW	1809	hFzd6L, mFzd6L
041S-H09	hFzd6L	YTFTSYYMH	418	GIINPNSGGTNYA	1114	CARESIAAPVRSYNWFDPW	1810	hFzd6L, mFzd6L
041S-A03	hFzd6L	YRFTGYYMH	419	GIINPSGGSTSYA	1115	CARDRKARGALWYW	1811	hFzd6L, mFzd6L
041S-A05	hFzd6L	YTFTGYYMH	420	GIINPNGGSANYA	1116	CARDRRAIYGMDVW	1812	hFzd6L, mFzd6L
041S-G05	hFzd6L	FTFSSYAMH	421	SYSSGNSGYTNYA	1117	CARSYSSGRAFDYW	1813	hFzd6L, mFzd6L
041S-D06	hFzd6L	FTFTNYYVH	422	GIINPSAGRTRYA	1118	CATAKVKHPRDDAFDIW	1814	hFzd6L, mFzd6L
041S-C07	hFzd6L	GRFSTYALS	423	GAIDPSGGSTNYA	1119	CARVLAVAGQYYFDYW	1815	hFzd6L, mFzd6L
041S-E08	hFzd6L	FSFSNYAMG	424	SAISSGSAYTYYA	1120	CARHKRTVTAFMDVW	1816	hFzd6L, mFzd6L
041S-C09	hFzd6L	FTFSSYAMH	425	AVISYDGSNKYYA	1121	CARDDIYSSSSVDYYYYGMDVW	1817	hFzd6L, mFzd6L
041S-A10	hFzd6L	FTFSSYAMH	426	AVISYDGSNKYYA	1122	CARDDIYSSSSVDYYYYGMDVW	1818	hFzd6L, mFzd6L
041S-C02	hFzd6L	YTFTDYYIH	427	GIINPSGGSTSYA	1123	CARHVGSVAHTYQNWFDPW	1819	hFzd6L, mFzd6L
041S-B03	hFzd6L	FTFSSYAMH	428	ZVISYDGSNKYYA	1124	CARDDIYSSSSVDYYYYGMDVW	1820	hFzd6L, mFzd6L
041S-F04	hFzd6L	YTFTGYHIH	429	GRITPIFGSADYA	1125	CARGFGYGDYSTYW	1821	hFzd6L, mFzd6L
041S-B05	hFzd6L	GTFSNYAIN	430	GWMNPNSGNTGYA	1126	CARVGYSSGWKDAFDIW	1822	hFzd6L, mFzd6L
041S-E06	hFzd6L	YTFTDYYMH	431	GIINPSGGTTSYA	1127	CARGGDSYYYYMDVW	1823	hFzd6L, mFzd6L
041S-D07	hFzd6L	YTFTSNNMH	432	GMINPSGGSTSYA	1128	CARGDYYGSGAGYW	1824	hFzd6L, mFzd6L
041S-B10	hFzd6L	YTFTSYYMH	433	GWMNPNSGNTGYA	1129	CARVFYDSSGYYYFDYW	1825	hFzd6L, mFzd6L
042S-F03	hFzd6L	ZZFTANYIZ	434	GRINHNSGGTNYA	1130	CARDQWKPYYFDFW	1826	hFzd6L, mFzd6L
041S-C10	hFzd6L	YTFTSYGIS	435	GGITPIFGTAKYA	1131	CARAVGRVGATLDYW	1827	hFzd6L, mFzd6L
041S-H10	hFzd6L	DSVSNNNAAWN	436	GRTYQRSKWFTYYA	1132	CARGNIVGAIDYW	1828	hFzd6L, mFzd6L
042S-B02	hFzd6L	YTFTANYIH	437	GRINPNSGGTNYA	1133	CARDQWKPYYFDSW	1829	hFzd6L, mFzd6L
042S-G03	hFzd6L	ZSFSSYVMZ	438	AVISYDGSNKYYA	1134	CARTATCGYYFDYW	1830	hFzd6L, mFzd6L
041S-D10	hFzd6L	FTFSSYZMH	439	AZIZYDGSNKZYA	1135	CAKEGWLLSYAFDIW	1831	hFzd6L, mFzd6L
041S-G11	hFzd6L	FTFSZYZMH	440	AVISYDGSNKYYA	1136	CVVRGDYW	1832	hFzd6L, mFzd6L
042S-C01	hFzd6L	FTFSSYAMH	441	AVISYDGSNKYYA	1137	CAKEGWLLSYAFDIW	1833	hFzd6L, mFzd6L
042S-A03	hFzd6L	FTFRRHAMH	442	SRINNDGRITSYA	1138	CASLIITENQAFDFW	1834	hFzd6L, mFzd6L
041S-B11	hFzd6L	FTFZRYZLZ	443	TVIZZZGSNKZXA	1139	CARTYRCGYSLDYW	1835	hFzd6L, mFzd6L
042S-A04	hFzd6L	FTFGDYAMZ	444	GFIRSKAYGGTTEYA	1140	CTTDSRWFDIW	1836	hFzd6L, mFzd6L
041S-C11	hFzd6L	FTFSSYAMH	445	AVISYDGSNKYYA	1141	CVVRGDYW	1837	hFzd6L, mFzd6L
042S-D03	hFzd6L	FTFSSYAMH	446	AVISYDGSNKZYA	1142	CAKEGWLLSYAFDIW	1838	hFzd6L, mFzd6L
042S-F04	hFzd6L	DSVSSSSAAWT	447	GRTYYRSKWYNDYA	1143	CVRGGYDFDSW	1839	hFzd6L, mFzd6L

042S-D01	hFzd6L	FTFSSYAMH	448	AVISYDGSNKYYA	1144	CARGGPFGSNW	1840	hFzd6L, mFzd6L
042S-H01	hFzd6L	FTFSSYAMH	449	AVISYDGSNKYYA	1145	CAKEGWLLSYAFDIW	1841	hFzd6L, mFzd6L
042S-C05	hFzd6L	FTFSSYAMH	450	AVISYDGSNKYYA	1146	CAKEGWLLSYAFDIW	1842	hFzd6L, mFzd6L
041S-E11	hFzd6L	FTFSZYZMZ	451	AVISYDGSNKYYA	1147	CVVRGDYW	1843	hFzd6L, mFzd6L
041S-B12	hFzd6L	FTFSSYAMH	452	AVISYDGSNKYYA	1148	CAKEGWLLSYAFDIW	1844	hFzd6L, mFzd6L
041S-G12	hFzd6L	FTFSSFGMH	453	AVISYDGSNKYYA	1149	CASTPGFW	1845	hFzd6L, mFzd6L
042S-E01	hFzd6L	DSVSSSSAAWT	454	GRTZYRSKWYNDYA	1150	CVRGGYDFDSW	1846	hFzd6L, mFzd6L
042S-B04	hFzd6L	FTFSTYDMH	455	AVISYDGSNKYYA	1151	CATRGRYFDYW	1847	hFzd6L, mFzd6L
041S-G10	hFzd6L	FTFSSYZMH	456	AZISYDGSNKZYA	1152	CASSPGYW	1848	hFzd6L, mFzd6L
042S-A02	hFzd6L	FTFSSYAMH	457	AVISYDGSNKYYA	1153	CAKEGWLLSYAFDIW	1849	hFzd6L, mFzd6L
042S-C03	hFzd6L	FTFSSYAMH	458	AVISYDGSNKYYA	1154	CVVRGDYW	1850	hFzd6L, mFzd6L
042S-C04	hFzd6L	FTFSSYAMH	459	AVISYDGSNKYYA	1155	CARTDTSGYYFDYW	1851	hFzd6L, mFzd6L
042S-H07	hFzd6L	FTFSSYAMH	460	AVISYDGSNKYYA	1156	CARGSTYYFDYW	1852	hFzd6L, mFzd6L
042S-G08	hFzd6L	FTFSSYAMS	461	SAISGSGGSTYYA	1157	CARAWRADAFDIW	1853	hFzd6L, mFzd6L
042S-H09	hFzd6L	FTFSSYAMH	462	AVISYDGSNKYYA	1158	CARGGKDW	1854	hFzd6L, mFzd6L
042S-D10	hFzd6L	YTFTSYYMH	463	GIINPSGGSTSYA	1159	CALRVPVITFGGVIGDDAFDIW	1855	hFzd6L, mFzd6L
042S-G10	hFzd6L	FTFSSYAMH	464	AVISYDGSNKYYA	1160	CARGGKDW	1856	hFzd6L, mFzd6L
042S-A08	hFzd6L	GSISSSSYYWG	465	GSIYYSGSTYYN	1161	CARYGHSSGWSFDYW	1857	hFzd6L, mFzd6L
042S-H08	hFzd6L	FTFSSYGMH	466	AVISYDGSNKYYA	1162	CATGGPIDYW	1858	hFzd6L, mFzd6L
042S-E09	hFzd6L	FTFSSYAMH	467	AVISYDGSNKYYA	1163	CASQSRGW	1859	hFzd6L, mFzd6L
042S-A06	hFzd6L	FTFSSYAMH	468	AVISYDGSNKYYA	1164	CVVRGDYW	1860	hFzd6L, mFzd6L
042S-F06	hFzd6L	FTFSZZZMH	469	YHHMZEADZZYA	1165	CARGGAGEW	1861	hFzd6L, mFzd6L
042S-B08	hFzd6L	FTFSSYAMH	470	AVISYDGSNKYYA	1166	CARTATSGYYFDYW	1862	hFzd6L, mFzd6L
042S-A09	hFzd6L	FTFSSYGMH	471	AVISYDGSNKYYA	1167	CATGGPIDYW	1863	hFzd6L, mFzd6L
042S-H10	hFzd6L	FTFSSYAMS	472	SGISGSGGNTYYA	1168	CATAGVGAVAGTIHLDAFDIW	1864	hFzd6L, mFzd6L
042S-D07	hFzd6L	FTFSSYZZH	473	AVISYZZSNKZYA	1169	CARTDTCGYYFDYW	1865	hFzd6L, mFzd6L
042S-B09	hFzd6L	FTFSSYZMH	474	AVISYDGSNKYYA	1170	CARGGKDW	1866	hFzd6L, mFzd6L
042S-A11	hFzd6L	FTFSSYAMT	475	ANIKTDGSEKYYV	1171	CAGGGALDYW	1867	hFzd6L, mFzd6L
042S-H06	hFzd6L	FTFSSYAMH	476	AVISYDGSNKYYA	1172	CVVRGDYW	1868	hFzd6L, mFzd6L
042S-E07	hFzd6L	FTFSSYAMH	477	AVISYDGSNKYYA	1173	CVVRGDYW	1869	hFzd6L, mFzd6L
042S-D08	hFzd6L	FTFSSYAMH	478	AVISYDGSNKYYA	1174	CANPTYGMDVW	1870	hFzd6L, mFzd6L
042S-F09	hFzd6L	FTFSSYGMH	479	SAISGSGGSTYYA	1175	CARDQGGATDYW	1871	hFzd6L, mFzd6L
042S-A10	hFzd6L	FTFIZYAMS	480	SGISGSSGNTYYA	1176	CAKGYSGSYSLYFDYW	1872	hFzd6L, mFzd6L
042S-C09	hFzd6L	FTFSSYAMS	481	SAISGSGGSTYYA	1177	CAKATANDAFDIW	1873	hFzd6L, mFzd6L

042S-F10	hFzd6L	FTFGGYAMS	482	GFIRSKTYGGTTEYA	1178	CSRGGSYAFDYW	1874	hFzd6L, mFzd6L
042S-D11	hFzd6L	FIFSZYAMS	483	SGISGSGDSTZYA	1179	CAKSSGGGFDLW	1875	hFzd6L, mFzd6L
042S-F07	hFzd6L	FTFSSYAMS	484	SAISGSGGSTYYA	1180	CAKVTVGASRSFDYW	1876	hFzd6L, mFzd6L
042S-E08	hFzd6L	FTFSSYAMH	485	SAISSNGGSTZYA	1181	CAKSTGSLYRAFDYW	1877	hFzd6L, mFzd6L
042S-B10	hFzd6L	FTFSSYAMS	486	SAISGSGGSTYYA	1182	CAKDSYYGSGSDDAFDIW	1878	hFzd6L, mFzd6L
042S-B11	hFzd6L	FTFSSYGMH	487	AVISYDGSNKYYA	1183	CATGGPIDYW	1879	hFzd6L, mFzd6L
042S-F11	hFzd6L	FTFSZYGMH	488	AVISZDGSNKZYA	1184	CAKVAPGLGSGARGYGMDVW	1880	hFzd6L, mFzd6L
042S-B07	hFzd6L	FTFSSYZMH	489	AVISYDGSNKXYA	1185	CVVRGDYW	1881	hFzd6L, mFzd6L
042S-G07	hFzd6L	GTFSSYAIS	490	GGIIPIFGTANYA	1186	CARGLFGVVIDPAW	1882	hFzd6L, mFzd6L
042S-F08	hFzd6L	NTFTNYGIH	491	GWINAGNGNTKYS	1187	CLRRAYSDYEVRGEEPW	1883	hFzd6L, mFzd6L
042S-C10	hFzd6L	FTFSSYGMH	492	AVISYDGSNKYYA	1188	CATGGPIDYW	1884	hFzd6L, mFzd6L
043S-D05	hFzd6L	FTFSZZZMH	493	AZISYDGSNKZYA	1189	CARGGPYSSGWIDYW	1885	hFzd6L, mFzd6L
043S-H04	hFzd6L	FTFSGYAMH	494	AVISYDGSNKYYA	1190	CARGPNYYDSSADYW	1886	hFzd6L, mFzd6L
043S-G08	hFzd6L	FTFSGYAMH	495	AVISYDGSNKYYA	1191	CARGPNYYDSSADYW	1887	hFzd6L, mFzd6L
043S-D09	hFzd6L	FTFSSYAMH	496	SAISSNGGSTYYA	1192	CARVSRGGDFDYW	1888	hFzd6L, mFzd6L
043S-E09	hFzd6L	FTFSSYAMH	497	AVISYDGSNKYYA	1193	CAKEGWLLSYAFDIW	1889	hFzd6L, mFzd6L
043S-F07	hFzd6L	FTFSSYAMH	498	AVISYDGSNKYYA	1194	CVVRGDYW	1890	hFzd6L, mFzd6L
043S-H07	hFzd6L	FTFSSYAMH	499	AVISYDGSNKYYA	1195	CVVRGDYW	1891	hFzd6L, mFzd6L
043S-F08	hFzd6L	FTZSZYAMZ	500	SAISGSGGSTYYA	1196	CAKATANDAFDIW	1892	hFzd6L, mFzd6L
043S-C09	hFzd6L	FTFSSYAMS	501	SAISGSGGSTYYA	1197	CAKDSYYGSGSDDAFDIW	1893	hFzd6L, mFzd6L
031S-G02	hFzd7ext	FTFSSYGMH	502	AVISYDGSNKYYA	1198	CAKGTTAGW	1894	hFzd7L
031S-A03	hFzd7ext	YTFASYYIH	503	GIINPSGGRTTYA	1199	CARERSSGSYGMDVW	1895	hFzd7L
031S-B03	hFzd7ext	YTFTSYYMH	504	GIINPSSGSTSYA	1200	CARDKGGYSLYW	1896	hFzd7L
031S-C03	hFzd7ext	YTFTSYDIN	505	GVIDPTGEATLYA	1201	CARGSSSGWYYFDYW	1897	hFzd7L
031S-D03	hFzd7ext	YTFTNYYMH	506	GIINPSGGSTSYA	1202	CAREGRLSYGMDAW	1898	hFzd7L
031S-E03	hFzd7ext	YTFTSYHVH	507	GRINPHTGGTNYA	1203	CAATPRWTTWFQHW	1899	hFzd7L
031S-F03	hFzd7ext	YTFRDYYMH	508	GVINPSGGITSYA	1204	CARDLENGAIYFQHW	1900	hFzd7L
031S-G03	hFzd7ext	YTFTAYYMH	509	GIINPTDGGTTYA	1205	CARHGKWEPSLVDPW	1901	hFzd7L
031S-H03	hFzd7ext	FTFSSSAMH	510	AAVSRSGGSTFYA	1206	CAQQYYVLGEYFDYW	1902	hFzd2L,7L
031S-A04	hFzd7ext	NTFIGYYVH	511	GWMNPNSGNTGYA	1207	CARGVDYMDVW	1903	hFzd7L
031S-C04	hFzd7ext	FTFSDYYMS	512	SSISSSSSYIYYA	1208	CARRIVGAAFDYW	1904	hFzd7L
031S-D04	hFzd7ext	HTLNSYYMH	513	GIINPRNGRTSYA	1209	CARDDKRTGTLDYW	1905	hFzd7L
031S-E04	hFzd7ext	FTFSSHGMH	514	SGINWNGGSTGYA	1210	CARVGNHDAFDIW	1906	hFzd7L
031S-F04	hFzd7ext	FTFSSYPMS	515	SAISGSGGSTYYA	1211	CAIRVRASGLFPNGMDVW	1907	hFzd2L,7L

031S-G04	hFzd7ext	YTVTRSYMH	516	GWMNPNSGNTZYA	1212	CATGIAVAGIPYDYW	1908	hFzd7L
031S-H04	hFzd7ext	YTFTGYYMH	517	GIINPSGGSTTYA	1213	CARDQYYYGSGSQPGMDVW	1909	hFzd7L
031S-A05	hFzd7ext	YTFTSYYMH	518	GIISPSGGGTSYP	1214	CASQDVEGALDYW	1910	hFzd7L
031S-B05	hFzd7ext	GTFSSHAIS	519	GIINARTGTTDYA	1215	CARDMGDIW	1911	hFzd7L
031S-C05	hFzd7ext	FTFSNAWMS	520	SSISRDSRYIYYA	1216	CAAGQGGYFDYW	1912	hFzd7L
031S-D05	hFzd7ext	FTFSDYYMS	521	SYISGDSGYTNYA	1217	CARGGGDFDYW	1913	hFzd7L
031S-E05	hFzd7ext	YTFTSYDIN	522	GWMIPNSGNTAYA	1218	CARGGQQLDYYYYYGMDVW	1914	hFzd7L
031S-F05	hFzd7ext	GTFTSYALN	523	GMINPSSGSTNYA	1219	CTRLRRSEYYFDYW	1915	hFzd2L,7L
031S-G05	hFzd7ext	GTFTNYHMH	524	GIINPSGGSTSYA	1220	CARDQWNIVGATYYYGMDVW	1916	hFzd7L
031S-A06	hFzd7ext	YTFTNYYMH	525	GIINPSRGNTNYA	1221	CARHGRGRDFGMDVW	1917	hFzd7L
031S-B06	hFzd7ext	YTFTTYYMH	526	GIINPSGGSTSYA	1222	CARDGSGYELDYW	1918	hFzd7L
031S-D06	hFzd7ext	DSFTTYYIH	527	GIINPSGGSTSYA	1223	CARDPTTVTPLGYYYGMDVW	1919	hFzd7L
031S-E06	hFzd7ext	YTFSTHYMH	528	GIINPSGGSTSYA	1224	CARDLVAGYYFDYW	1920	hFzd7L
031S-F06	hFzd7ext	YTFTSHAIS	529	GWISAYNGNTKYV	1225	CTTRVGRYPTYYYGMDVW	1921	hFzd7L
031S-G06	hFzd7ext	FTFSSYAMH	530	AGTSGSGESRDYA	1226	CARGQVLRFFDVW	1922	hFzd1L,2L,7L
031S-A07	hFzd7ext	GTFSSYAIS	531	GWMNPNSGYTGYA	1227	CARTYGDYFDYW	1923	hFzd7L
031S-C07	hFzd7ext	GTFTGYAIN	532	GWMNPNSGNTGYA	1228	CARLTRKGADYYFDYW	1924	hFzd1L,2L,7L
031S-E07	hFzd7ext	FTFSSYWMH	533	STISASGGNTYYA	1229	CARGGSNYYYYGMDVW	1925	hFzd1L,2L,7L
031S-H07	hFzd7ext	YTFTSYYMH	534	GIINPSGGSTSYA	1230	CARGQGYMDVW	1926	hFzd7L
031S-A08	hFzd7ext	YTFTGYYMH	535	GIINPSDGETSYA	1231	CARDRPYYDGYGMDVW	1927	hFzd2L,7L
031S-B08	hFzd7ext	YTFTKYYMH	536	GIINPVSGTTSYA	1232	CARVRRHGGHSDYW	1928	hFzd7L
031S-C08	hFzd7ext	GTFNNYALS	537	GIINPSGGSTSYA	1233	CAHIARKQYYFDYW	1929	hFzd2L,7L
031S-D08	hFzd7ext	YTFTNYYMH	538	GIINPSGGSTSYA	1234	CARGSYPLAVGATLYYYYGMDVW	1930	hFzd7L
031S-E08	hFzd7ext	YTFTGHYMH	539	GIINPSGGATIYA	1235	CTTDGGLGYAFDIW	1931	hFzd7L
031S-F08	hFzd7ext	FTFSSYGMH	540	AGVSYDKSQEYYA	1236	CTRPAKYGDLDYW	1932	hFzd7L
031S-G08	hFzd7ext	YTFSDHYMH	541	GWMNPKSGNTGYS	1237	CAKGVDTFDYW	1933	hFzd7L
031S-H08	hFzd7ext	FTFSSYGMS	542	SAISASGGYTYYA	1238	CARVGYYYGMDVW	1934	hFzd1L,2L,7L
032S-G01	mFzd7L	YTFTGYYMH	543	GIINPSGGGTSYA	1239	CARDSGSNGYAFDIW	1935	hFzd7L, mFzd7L
032S-H01	mFzd7L	YTFTDYYIQ	544	GIINPSGGITSYA	1240	CAKDRRQLVRSAWFDPW	1936	hFzd7L, mFzd7L
032S-A02	mFzd7L	YTFSGYGIS	545	GWMNPYSGNTGYA	1241	CARGPARRHYYYGMDVW	1937	hFzd7L, mFzd7L
032S-B02	mFzd7L	YPFIGXYLH	546	GWMNPKSGNTGYA	1242	CAKDLIAAAGTGYGMDVW	1938	hFzd7L, mFzd7L
032S-F02	hFzd7L	FTFSNAWMS	547	STIRASGGNTYYA	1243	CASGVYGMDVW	1939	hFzd7L
032S-D02	hFzd7L	YTFTNYYMH	548	GVINTGGGSVTYA	1244	CARDLLGAVGYGMDVW	1940	hFzd7L, mFzd7L
032S-H02	hFzd7L	HTFTSYYMH	549	GIINPSGGSTSYA	1245	CARDLTEAPTGTTRYYYYGMDVW	1941	hFzd7L, mFzd7L

032S-A03	hFzd7L	YTFTAYYVH	550	GIINPSGGYSTYA	1246	CARQYYDFWSGYPLSGMDVW	1942	hFzd7L
049S-B02	hFzd7L	YTFTGYYMH	551	GWMNPNSGNTGYA	1247	CTTELDILTGYGFDYW	1943	hFzd7L, mFzd7L
049S-D02	hFzd7L	DTFTRYYIH	552	GIINPSSGSTSYA	1248	CARDLRDIVGATRHYYYYGMDVW	1944	hFzd7L, mFzd7L
049S-F02	hFzd7L	YTFTGYYMH	553	GWMSPNSGNAGFA	1249	CASQYNWNDGYYYGMDVW	1945	hFzd7L, mFzd7L
049S-H02	hFzd7L	YTFTSYYMH	554	GIINPSGGSTSYA	1250	CARDRGSSGYYLGYW	1946	hFzd7L, mFzd7L
049S-A03	hFzd7L	YTLTSFYMH	555	GWINPHSGDTYYA	1251	CARELGYGWFDPW	1947	hFzd7L, mFzd7L
049S-B03	hFzd7L	FTFSSYWMS	556	SAISSSGASTYYA	1252	CARGRDIGGIFDYW	1948	hFzd7L, mFzd7L
049S-C03	hFzd7L	YTFTTYSMQ	557	GWMSPNSGNTGYA	1253	CASGIGYYYGMDVW	1949	hFzd7
049S-E03	hFzd7L	YTFTGYFLH	558	GWISAYNGNTNYA	1254	CARDRSGYFDLW	1950	hFzd7L, mFzd7L
049S-F03	hFzd7L	NTFKGYYMH	559	GWMNVHTGNTGYA	1255	CAKVGGYSSSWYPSYYYGMDVW	1951	hFzd7L, mFzd7L
049S-H03	hFzd7L	YTFPAXYMH	560	GWISAYNGNTNYA	1256	CARDSLAGWFDPW	1952	hFzd7L, mFzd7L
049S-A04	hFzd7L	YTFTNYYVH	561	GIINPSGDGTNYA	1257	CARDQYGGYAFDYW	1953	hFzd7L, mFzd7L
049S-B04	hFzd7L	YTFTSYYMH	562	GWISAYNGNTNYA	1258	CVRSSGGYLDLW	1954	hFzd7L, mFzd7L
049S-C04	hFzd7L	YTFTGYYMH	563	GIINPSGGGTSYA	1259	CARDSGSNGYAFDIW	1955	hFzd7L, mFzd7L
15G4-4	mFzd8L	GYTFTDYYMN	564	GDINPNNGGSRYN	1260	CAREGRYGYDGAWFAYW	1956	mFzd8L
027S-E5	hFzd8	GTFSSYAIS	565	GMINPSGGSTTYA	1261	CARQAGLHCSSTSCYLGNWFDPW	1957	hFzd8
037S-A01	hFzd9L	YKFNSNAMN	566	GGIIPIFGTANYA	1262	CARFGWYYYGMDVW	1958	hFzd9L
050S-A01	hFzd9L	GTFNIYAIS	567	GWINPNSGNTGYA	1263	CAKYSSSWYGQDQHDAFDIW	1959	hFzd9, mFzd9
050S-B01	hFzd9L	YTFTDYHMH	568	GWMNPNSGNTGYA	1264	CARDDPYGYFLMDFW	1960	hFzd9, mFzd9
050S-C01	hFzd9L	YTFTSYYMH	569	GIINPNGGZTSYA	1265	CARDSDYDWSWFYPW	1961	hFzd9, mFzd9
050S-D01	hFzd9L	YTFTSYYMN	570	GWINPNTGDTSFA	1266	CAKEADGNYFYGLDVW	1962	hFzd9, mFzd9
050S-E01	hFzd9L	YSFTSYGIT	571	GGIIPVFVTPRYA	1267	CTTSLYYDSSGYYSSPYYYYGMDVW	1963	hFzd9, mFzd9
050S-F01	hFzd9L	YTVTDYYMH	572	GIINPYGGGTSYG	1268	CAREYSSSLVFDLW	1964	hFzd9, mFzd9
050S-G01	hFzd9L	YTFTTYYIH	573	GWINPNGGZTSYA	1269	CARDRCYDFW	1965	hFzd9, mFzd9
050S-H01	hFzd9L	STFISAYMH	574	GWMNPNSGNTGYA	1270	CATSSSGEHYYMDVW	1966	hFzd9, mFzd9
050S-A02	hFzd9L	YTFTSYYMH	575	GIINPNGGTTSYA	1271	CARDSDYDWSWFYPW	1967	hFzd9, mFzd9
050S-B02	hFzd9L	YTFTSYYMH	576	GIINPSGGSTNYA	1272	CAKGSPYDWGYFDYW	1968	hFzd9, mFzd9
050S-C02	hFzd9L	YTFTSYDIN	577	GWIDPSSGATDYA	1273	CARDGGLLRNYYYGMDVW	1969	hFzd9, mFzd9
050S-D02	hFzd9L	GTFDTFAIS	578	GWINPNSGGTNYA	1274	CAKHWVGKGMDVW	1970	hFzd9, mFzd9
050S-E02	hFzd9L	YTFTSYDIN	579	GIIDPSGGSTDYA	1275	CARDGVVPAAQLYYYYGMDVW	1971	hFzd9, mFzd9
050S-F02	hFzd9L	YTFTGYFIH	580	GIINPSSGNTNYA	1276	CAKGRYSGGWGDFDWW	1972	hFzd9, mFzd9
050S-G02	hFzd9L	YTFTSYYMH	581	GRINPNGGNTSYA	1277	CARDIYNYYYYGMDGW	1973	hFzd9, mFzd9
050S-H02	hFzd9L	YTFTGYYMH	582	GWMNPNSGNTGYA	1278	CARDYSRYYYGMDVW	1974	hFzd9, mFzd9
050S-A03	hFzd9L	YTFTSYYMH	583	GIINPSGGSTSYA	1279	CARESGYDWSWFDPW	1975	hFzd9, mFzd9

050S-B03	hFzd9L	YTFTNYYVH	584	GIINPSGGNTSYA	1280	CARHRDNWNYDGMDVW	1976	hFzd9, mFzd9
050S-C03	hFzd9L	YTFPNYYMH	585	GIINPSGAGTTYA	1281	CAKEHSGNCYAFDIW	1977	hFzd9, mFzd9
050S-D03	hFzd9L	YTFTSYYMH	586	GIINPZGGSTSYA	1282	CARDSGYDWSWFDPW	1978	hFzd9, mFzd9
050S-E03	hFzd9L	YTFTSYYIH	587	GWINPZSGDTIYA	1283	CARDKCNSNYCLINGMDVW	1979	hFzd9, mFzd9
050S-F03	hFzd9L	YTFTSYYMH	588	GWINPSSGSTTYA	1284	CARDLSGNWYGALDYW	1980	hFzd9, mFzd9
050S-G03	hFzd9L	YTFTSYYMH	589	GIINPNGGZTSYA	1285	CARDSDYDWSWFYPW	1981	hFzd9, mFzd9
050S-H03	hFzd9L	YTFTNYYIH	590	GIINPZGGNTIYA	1286	CAKDRDNCYYYYLDVW	1982	hFzd9, mFzd9
050S-A04	hFzd9L	YTVTDYYMH	591	GIINPYGGGTSYG	1287	CAREYSSSLVFDLW	1983	hFzd9, mFzd9
050S-B04	hFzd9L	YTFTRYAMN	592	GWMNPNSGDTGYA	1288	CARGPAVGASYYYYGMDVW	1984	hFzd9, mFzd9
050S-C04	hFzd9L	YTFTSYYMH	593	GIINPNSGSTSYA	1289	CARGFRDDFSFSDLW	1985	hFzd9, mFzd9
050S-D04	hFzd9L	YTFTSYYMH	594	GIINPNGGTTSYA	1290	CARESGYDWSWFDPW	1986	hFzd9, mFzd9
050S-E04	hFzd9L	YTZTDYYMH	595	GIINPYGGGTSYG	1291	CAREYSSSLVFDLW	1987	hFzd9, mFzd9
050S-F04	hFzd9L	YTFTDYYMH	596	GWMNPNSDNTGYA	1292	CAREGYYYGMDVW	1988	hFzd9, mFzd9
050S-G04	hFzd9L	YSFTGYYMH	597	GWTDPISGDTSYA	1293	CARNPLYGDYGAIDYW	1989	hFzd9, mFzd9
050S-H04	hFzd9L	YTFTSYYMH	598	GIINPSGGSTSYA	1294	CARDRDSDYYEWGYFDLW	1990	hFzd9, mFzd9
050S-A05	hFzd9L	YTFTSYYMH	599	GIINPSGGYTTYA	1295	CARGAESSGWSQFDYW	1991	hFzd9, mFzd9
050S-B05	hFzd9L	YTFTSYYMH	600	GIINPSGGSTSYG	1296	CARGGSYDFGAFDIW	1992	hFzd9, mFzd9
050S-C05	hFzd9L	YAFTSYYVH	601	GIINPSEGSTNYA	1297	CARGENSDWGAFDIW	1993	hFzd9, mFzd9
050S-D05	hFzd9L	YTFTDYYMH	602	GIINPNGGSTSYA	1298	CARESGYYPSTSNDAFDIW	1994	hFzd9, mFzd9
050S-E05	hFzd9L	YTFTGYYMH	603	GIINPRVGSTTNA	1299	CAKGASGHDWGIFDYW	1995	hFzd9, mFzd9
050S-F05	hFzd9L	YTFTSYFMH	604	GWINPNSGATTYA	1300	CARDLVWASSGWGMDVW	1996	hFzd9, mFzd9
050S-G05	hFzd9L	YTFTSYYMH	605	GWMNPNSGDTGYA	1301	CARDQGWAGVPAADYYYYGMDVW	1997	hFzd9, mFzd9
050S-H05	hFzd9L	YTFTSYYMH	606	GIINPTVGSTTYA	1302	CAKGWDSSGWANFDYW	1998	hFzd9, mFzd9
050S-A06	hFzd9L	YTFTGYYMH	607	GVINPSGGSTTYA	1303	CARDRSSWPDYYYYGMDVW	1999	hFzd9, mFzd9
050S-B06	hFzd9L	YTFTSYFMH	608	GWINPNSGATTYA	1304	CARDLVWASSGWGMDVW	2000	hFzd9, mFzd9
050S-C06	hFzd9L	YTVTSHYMN	609	GWMNPYTGNTGFA	1305	CAREAEGNQIYGMDVW	2001	hFzd9, mFzd9
050S-D06	hFzd9L	GTFSSYAIS	610	GIINPRDGDTVYA	1306	CARDVTDYGDYVASWYFDLW	2002	hFzd9, mFzd9
050S-E06	hFzd9L	YTFTNYYMH	611	GWINPNSGATTYA	1307	CARDLTPDYYGAADYW	2003	hFzd9, mFzd9
050S-F06	hFzd9L	GAFSSYAIS	612	GWMSPNSGDTGYA	1308	CARHAEGRSADYW	2004	hFzd9, mFzd9
050S-G06	hFzd9L	YTVTDYYMH	613	GZISPYZGGTSYG	1309	CAREYSSSVVFDLW	2005	hFzd9, mFzd9
050S-A07	hFzd9L	YTFTGYYMH	614	GWINPNNGATNYA	1310	CAKDKTYYDFWSGYGFDYW	2006	hFzd9, mFzd9
050S-B07	hFzd9L	YTFTTYYVH	615	GIINPSSGSTTYA	1311	CAKDRVYGDYGDAFDIW	2007	hFzd9, mFzd9
050S-D07	hFzd9L	YTFTSYYMH	616	GIVNPSSGSTTYA	1312	CARDRDPYYYYYGMDVW	2008	hFzd9, mFzd9
050S-E07	hFzd9L	YTFTGYYMH	617	GWTZPISGDTNYA	1313	CAKNPLYGDCGAFDYW	2009	hFzd9, mFzd9

050S-F07	hFzd9L	YTVTDYYMH	618	GIINPYGGGTSYG	1314	CAREYSSSLVFDLW	2010	hFzd9, mFzd9
050S-G07	hFzd9L	FTFSSYXMS	619	SYISGDSGYTNYA	1315	CARGVAAADYW	2011	hFzd9, mFzd9
050S-A08	hFzd9L	YSFTZYYMH	620	GWTDHISGDTSYA	1316	CARNPLYGDYGAIDYW	2012	hFzd9, mFzd9
050S-B08	hFzd9L	YTFTSYYIH	621	GIINPSGGTTTYA	1317	CARDSSGWHPIPWGYFDLW	2013	hFzd9, mFzd9
050S-C08	hFzd9L	YTFTGYYMH	622	GWMNPNSGNTGYA	1318	CAREEGSGWYGMDVW	2014	hFzd9, mFzd9
050S-D08	hFzd9L	YTFTSYYMH	623	GIINPNGGTTTYA	1319	CARDIDYDWSWFYPC	2015	hFzd9, mFzd9
050S-E08	hFzd9L	YTFTGYYMH	624	GVINPNGGSTTYA	1320	CAKDIGASRYYYMDVW	2016	hFzd9, mFzd9
050S-F08	hFzd9L	YTLTSYYIH	625	GIINPNSGGTNYA	1321	CARHKAAAAGTQYYNGMDVW	2017	hFzd9, mFzd9
050S-G08	hFzd9L	YTFTSYYMH	626	GVINPTAGDTTYA	1322	CARDISWFGPMDVW	2018	hFzd9, mFzd9
050S-H08	hFzd9L	YTVTDYYMH	627	GIINPYGGGTSYG	1323	CAREYSSSLVFDLW	2019	hFzd9, mFzd9
050S-A09	hFzd9L	YTFTSYYMH	628	GIINPNGGZTSYA	1324	CARDSGYDWSWFYPC	2020	hFzd9, mFzd9
050S-B09	hFzd9L	YTFTZYYMH	629	GIINPYGGGTSYG	1325	CAREYSSSLVFDLW	2021	hFzd9, mFzd9
050S-C09	hFzd9L	YTFTSYYMH	630	GRINPNTGGTNYA	1326	CAKDLTYDFWSGWGMDVW	2022	hFzd9, mFzd9
050S-D09	hFzd9L	YTFTDYYMH	631	GIINPYGGGTSYG	1327	CAREYSSSLVFDLW	2023	hFzd9, mFzd9
050S-E09	hFzd9L	YTFTDYYIH	632	GWINLNSGGTNSG	1328	CARDRDRYSYGSGDYW	2024	hFzd9, mFzd9
050S-F09	hFzd9L	YTFTGNFIH	633	GIINPSSGNTNYA	1329	CAKGRYSSGWGDFDYW	2025	hFzd9, mFzd9
050S-G09	hFzd9L	YTVTDYYMH	634	GIINPYGGGTSYG	1330	CAREYSSSLVFDLW	2026	hFzd9, mFzd9
050S-H09	hFzd9L	GTFSSYAIS	635	GWINPNSGGTNYA	1331	CARGRYYGSGSYHFDYW	2027	hFzd9, mFzd9
050S-A10	hFzd9L	YTFTSYDIN	636	GWINPNSGATNYA	1332	CARGTMTTWYLFDYW	2028	hFzd9, mFzd9
050S-B10	hFzd9L	YTFTSYYMH	637	GIINPZGGTTSYA	1333	CARDSGYDWSCFYPW	2029	hFzd9, mFzd9
050S-C10	hFzd9L	YTFTDYYMH	638	GIINPYGGGTSYG	1334	CAREYSSSLVFDLW	2030	hFzd9, mFzd9
050S-D10	hFzd9L	YTFTGYYMH	639	GWINPNNGATNYA	1335	CAKDKTYYDFWSGYGFDYW	2031	hFzd9, mFzd9
050S-E10	hFzd9L	YTFTZYYMH	640	ZIINPSZZSTSZA	1336	YSRGSGYDWSWFDPW	2032	hFzd9, mFzd9
050S-F10	hFzd9L	YSFTSYFVH	641	GIINPSGGATIYA	1337	CARGGVRGYSGYDPFDYW	2033	hFzd9, mFzd9
050S-G10	hFzd9L	YSFTSYYMH	642	GRMNPNGGNTGYA	1338	CARDKYLYYYGMDVW	2034	hFzd9, mFzd9
050S-H10	hFzd9L	YTFTSHYMH	643	GIVNPSSGSTTYA	1339	CARMGASGSGWYHWFDPW	2035	hFzd9, mFzd9
050S-A11	hFzd9L	YTFSDYYIH	644	GIINPIDGGTTYA	1340	CARDMTVGNWGYFDYW	2036	hFzd9, mFzd9
050S-B11	hFzd9L	YTFTNYYMH	645	GIINPSGGSTSYA	1341	CARELDDYGDYVAGFDPW	2037	hFzd9, mFzd9
050S-C11	hFzd9L	YTFZSYYMH	646	ZIINPSGGSTSYA	1342	CARGSGYDWSWLDPW	2038	hFzd9, mFzd9
050S-D11	hFzd9L	YTFTSYYMH	647	GIINPSGGTTSYA	1343	CARDSGYDWSWFDPW	2039	hFzd9, mFzd9
050S-E11	hFzd9L	YTVTDYYMH	648	GIINPYGGGTSYG	1344	CAREYSSSLVFDLW	2040	hFzd9, mFzd9
050S-F11	hFzd9L	YTFTSYYMH	649	GIINPVGGSTTYA	1345	CARDSFSAAGMFGWFDPW	2041	hFzd9, mFzd9
050S-G11	hFzd9L	YTFPNYYMH	650	GIINPSGGSTTYA	1346	CARGHSYDWGAFDIW	2042	hFzd9, mFzd9
050S-H11	hFzd9L	YTFTNYYLH	651	GIINPSGGSTSYA	1347	CARGADSSGWSDFQHW	2043	hFzd9, mFzd9

050S-A12	hFzd9L	YTFTSYYMH	652	GZINPZGGTTTYA	1348	CARDSGYDWSCYYPW	2044	hFzd9, mFzd9
050S-B12	hFzd9L	YSFTGFYMH	653	GWISPYNGNAKYA	1349	CAREGYSYGYDYW	2045	hFzd9, mFzd9
050S-C12	hFzd9L	YTFTSYYMH	654	GWINPNTGGTNYA	1350	CAKDLTYDFWSGWGMDVW	2046	hFzd9, mFzd9
050S-D12	hFzd9L	YSFTSYYMH	655	GWMNPNSGNTGYA	1351	CARDKYLYYYGMDVW	2047	hFzd9, mFzd9
050S-E12	hFzd9L	ZTFSNYAIZ	656	GWINPZRGDTMYA	1352	CAKDQYSNYYYYYYGMDVW	2048	hFzd9, mFzd9
050S-F12	hFzd9L	YTZTDYYMH	657	GIISPYGGGTSYG	1353	CARENSSSLVFDLW	2049	hFzd9, mFzd9
050S-G12	hFzd9L	GTFSNYAIS	658	GWINPKRGDTMYA	1354	CAKDQYSNYYYYYYGMDVW	2050	hFzd9, mFzd9
051S-A01	hFzd9L	YTFTGHYMH	659	GVINPSGGSTSYA	1355	CARDRAGDYDGWGYFDLW	2051	hFzd9, mFzd9
051S-B01	hFzd9L	YTFTSNYVH	660	GIINPSGGSTSYA	1356	CARQRDNWNYDGMDVW	2052	hFzd9, mFzd9
051S-C01	hFzd9L	YTFTSYYVH	661	GIINPSIGSTTYA	1357	CARGADSSGWSDFQHW	2053	hFzd9, mFzd9
051S-E01	hFzd9L	YTFTNSYIH	662	GWMSPNSGATNYA	1358	CAREIAAAEYIDYW	2054	hFzd9, mFzd9
051S-F01	hFzd9L	YTFTSYYMH	663	GIINPSGGSTSYA	1359	CARGSGYDWSWFDPW	2055	hFzd9, mFzd9
051S-G01	hFzd9L	YTFTNYYIN	664	GIINPSDGSTTYA	1360	CARQPKGYYYYGMDVW	2056	hFzd9, mFzd9
051S-H01	hFzd9L	YTFTGYYMH	665	GWINPNSGNTGYA	1361	CARDDSSGYYGMDVW	2057	hFzd9, mFzd9
051S-A02	hFzd9L	YTFADYNLH	666	GRIIPILGIANYA	1362	CARQFEFW	2058	hFzd9, mFzd9
046S-C02	hFzd10L	YTFTSYDMH	667	GWINPNSGGTNYA	1363	CVVFGSHNLDYW	2059	hFzd10L, mFzd10L
046S-E02	hFzd10L	YTFTSYYMH	668	GWVNPNIGGTNYE	1364	CAAGADVW	2060	hFzd10L, mFzd10L
046S-H02	hFzd10L	FTFSSYWMH	669	ALISYSGSEKYYA	1365	CARDSYGDYPYNWFDPW	2061	hFzd10L, mFzd10L
046S-A03	hFzd10L	YTFTNYYIH	670	GWMNPNSGYTGYA	1366	CARGDYGDYAGNYFDYW	2062	hFzd10L, mFzd10L
046S-F03	hFzd10L	YTFTHHSIH	671	GRISPHDGGTIYA	1367	CASGGTTYYYYGMDVW	2063	hFzd10L, mFzd10L
046S-B04	hFzd10L	GTFSSYAIS	672	GGIIPIFGTANYA	1368	CARVGGGMDVW	2064	hFzd10L, mFzd10L
046S-A05	hFzd10L	LSFGDYAIH	673	SAIGAGGGTYYA	1369	CARDEDGSGWLDYW	2065	hFzd10L, mFzd10L
046S-G01	hFzd10L	FTFSSYGMH	674	SAISSSGTDIYYA	1370	CARGGSYYVDYGMDVW	2066	hFzd10L
046S-A02	hFzd10L	FTFSSSAMH	675	SGISGSGYTTYYA	1371	CTTDGMDVW	2067	hFzd10L
046S-B03	hFzd10L	FSFTRYDMH	676	SGISWNSGSIGYA	1372	CARGGLGFDYW	2068	hFzd10L
046S-A04	hFzd10L	YTFTDYYMH	677	GVINPISGTVTYA	1373	CARGGSYQAFDYW	2069	hFzd10L
046S-C05	hFzd10L	YTLASYGIS	678	GWINPNSGGTHYA	1374	CARDGYDFWSGYPNYYYYYGMDVW	2070	hFzd10L, mFzd10L
046S-F05	hFzd10L	FSFRSYAMT	679	SDVSGSGGGTYYA	1375	CARDGRTGTRYYYYMDVW	2071	hFzd10L, mFzd10L
046S-A06	hFzd10L	FTFDDYAMH	680	SVISWDGSIQYYA	1376	CARDPLYGMDVW	2072	hFzd10L
046S-G06	hFzd10L	GTFSSYAIS	681	GWMNPNNGDTNYA	1377	CARENYGDDDYYYYGMDVW	2073	hFzd10L, mFzd10L
046S-D07	hFzd10L	FTFSSYGMH	682	SAISGSGGSTYYA	1378	CARQENHYYGMDVW	2074	hFzd10L
046S-E07	hFzd10L	YTFTNYYMH	683	GIINPNSGGTNYA	1379	CARMYSSSDGMDVW	2075	hFzd10L
046S-F07	hFzd10L	FTFSSHAMH	684	AVMSYDGRHEYYA	1380	CARNIAAAAYGMDVW	2076	hFzd10L, mFzd10L
046S-G07	hFzd10L	FTFSSHAMH	685	AVMSYDGRHEYYA	1381	CARSIAAAAYGMDVW	2077	hFzd10L, mFzd10L

046S-H07	hFzd10L	YTFTSYYVH	686	GIINPSGGSTSYA	1382	CARDPGFHYGSGSYYNVSVGWFDPW	2078	hFzd10L, mFzd10L
046S-E08	hFzd10L	YTFTSYYMH	687	GGIIPMFGQTNYA	1383	CARSGYSGYDPFDYW	2079	hFzd10L, mFzd10L
046S-G08	hFzd10L	YTFTENEMH	688	GWINPNSGNRGYA	1384	CARVGITGTTGDYYGMDVW	2080	hFzd10L
046S-A09	hFzd10L	GTFSSLDIN	689	GWMNPNSGNTGYA	1385	CARGADYW	2081	hFzd10L
046S-F09	hFzd10L	FTFSSYGIH	690	SAIGTGGGTYYA	1386	CARGNSAVAYGMDVW	2082	hFzd10L
046S-D10	hFzd10L	GTFTSYPIS	691	GIIRTGNGNTAYA	1387	CASEVLGAEYFQIW	2083	hFzd10L, mFzd10L
046S-F10	hFzd10L	GTFSSYAIS	692	GVINLSGGTTSYA	1388	CARDLEQLADKYYYYGMDVW	2084	hFzd10L, mFzd10L
046S-G10	hFzd10L	YTFSDYYMY	693	GIINPSGGSTSYA	1389	CATEPRWAAGRAFDIW	2085	hFzd10L, mFzd10L
046S-D11	hFzd10L	YTFTSYYMH	694	GWMNPNSGNTGYA	1390	CARMYGSGYGMDVW	2086	hFzd10L, mFzd10L
046S-F11	hFzd10L	YTFTNYDIN	695	GWMNRNSGNTGYA	1391	CARPPVCYSGYDCPYYFDYW	2087	hFzd10L, mFzd10L
046S-G11	hFzd10L	LSVSNNYMS	696	SAISGSGGSTYYA	1392	CARDHAVYGMDVW	2088	hFzd10L
046S-E12	hFzd10L	GTFSSYAFS	697	GWINPNSGGTDYA	1393	CAREDYYYGMDVW	2089	hFzd10L, mFzd10L
046S-G12	hFzd10L	FTFSDYYMS	698	GFIRSKAYGGTTEYA	1394	CASVDEGYW	2090	hFzd10L, mFzd10L
047S-A01	hFzd10L	YTFANYGIS	699	GVIYPGDSDTRYS	1395	CTSADAYYYYGMDVW	2091	hFzd10L, mFzd10L
047S-B01	hFzd10L	YTFTSYYIH	700	GGIIPVFGTPNYA	1396	CVLEGRVQHW	2092	hFzd10L
047S-E01	hFzd10L	FTFSSYXMS	701	SAIGTGGGTYYA	1397	CARDSYGMDVW	2093	hFzd10L, mFzd10L
047S-A02	hFzd10L	FTFSSYWMH	702	AVLSYDARNTYYA	1398	CARDYYGSLDFW	2094	hFzd10L
047S-C02	hFzd10L	FTFSSYGMH	703	SAIGTGGGTYYA	1399	CARDRVVNDW	2095	hFzd10L
047S-E02	hFzd10L	YTFTDYYMH	704	GWMNPNSGDTGYA	1400	CARQVPSSSAHYYYGMDVW	2096	hFzd10L, mFzd10L
047S-F02	hFzd10L	FTFSSYXMT	705	SAIGTGGGTYYA	1401	CARAYYGFDYW	2097	hFzd10L, mFzd10L
047S-F03	hFzd10L	FTVGSWYMS	706	SGLSGSGDTSYYA	1402	CARDTHYGMDVW	2098	hFzd10L, mFzd10L
047S-G03	hFzd10L	YTFTSYYLH	707	GIINPSGGSTSFA	1403	CARWNEGFGVVTGDYFDYW	2099	hFzd10L
047S-D04	hFzd10L	YTFTGYYMH	708	GMINPSGGSTNYA	1404	CAREGGDYIFDYW	2100	hFzd10L, mFzd10L
047S-E04	hFzd10L	FTFDDYAMH	709	AVISYDGSNKYYA	1405	CATGYCSGGSCYLTGYW	2101	hFzd10L
047S-H04	hFzd10L	YTFTNYYMH	710	GWMNPNSGGTNYA	1406	CARDPGNYYYYGMDVW	2102	hFzd10L, mFzd10L
047S-C05	hFzd10L	FTFSRHGMH	711	SAMSGSGSYKYYA	1407	CARVGSGYDFFYYMDVW	2103	hFzd10L
047S-E05	hFzd10L	GTFSSYAIS	712	GWVNPTSGNTGYA	1408	CARESGDYDEALDYW	2104	hFzd10L, mFzd10L
047S-F05	hFzd10L	YTFTSYYMH	713	GMINPNGGGTTYT	1409	CTTDRGDLW	2105	hFzd10L, mFzd10L
047S-G05	hFzd10L	FTVSPYWMT	714	AVISYDGSNKYYA	1410	CARAYNSWFDPW	2106	hFzd10L, mFzd10L
047S-C06	hFzd10L	FTFSSYXMS	715	SSISSSSSYIYYA	1411	CARDHDDYGMDVW	2107	hFzd10L, mFzd10L
047S-E06	hFzd10L	FTFSDYWMS	716	SAISGSGGSTYYA	1412	CARDGDYYGMDAW	2108	hFzd10L, mFzd10L
047S-F06	hFzd10L	FTFSSYAMH	717	GFIRSKAYGGTTEYA	1413	CARGDYW	2109	hFzd10L, mFzd10L
047S-G06	hFzd10L	YTFTTSYIH	718	GIINPSGGSTSYA	1414	CATAIREDGFDYW	2110	hFzd10L, mFzd10L
047S-A07	hFzd10L	FTFSSSAKH	719	STISSDGRTYYA	1415	CAKGRAYYYDSSGLLPDW	2111	hFzd10L, mFzd10L

047S-B07	hFzd10L	FTFSGYGMH	720	SAIGTGGGTYYA	1416	CARVRPYYYYYGMDVW	2112	hFzd10L
047S-C07	hFzd10L	FTFSSYXMS	721	SVISTSGDTVLYT	1417	CARGRLGGYFDLW	2113	hFzd10L, mFzd10L
047S-F07	hFzd10L	FTFSSYXMS	722	TLMSSDGNEEYYA	1418	CTTADYW	2114	hFzd10L, mFzd10L
047S-G07	hFzd10L	YTFTNYYMH	723	GWMNPNSGNTGYA	1419	CARMYSSSDGMDVW	2115	hFzd10L
047S-H07	hFzd10L	YTFTGYYMH	724	GWVNPNSGNTGYA	1420	CARDGWEQHARSGYYYYGMDVW	2116	hFzd10L, mFzd10L
047S-A08	hFzd10L	YTFTNYYMH	725	GWMNPNSGGTNYA	1421	CARDPGNYYYYGMDVW	2117	hFzd10L, mFzd10L
047S-C08	hFzd10L	FTFSNHYTS	726	SAIGTIDDTYYS	1422	CTTDYGWLGYW	2118	hFzd10L, mFzd10L
047S-D08	hFzd10L	FTFSSYXMS	727	SGISANGATTYYA	1423	CARDHDYYGMDVW	2119	hFzd10L, mFzd10L
047S-B11	hFzd10L	DSVSSNSAAWN	728	GRTYFRSKWYTEYA	1424	CVRGGYDFDSW	2120	hFzd10L, mFzd10L
047S-E12	hFzd10L	FTFSSYGMH	729	AAISYDGSNKYFA	1425	CARDGGKNGWHFDYW	2121	hFzd10L, mFzd10L

Table 2: cont. (light chain CDRs)

Clone ID	Antigen	CDRL1	CDRL1 SEQ ID	CDRL2	CDRL2 SEQ ID	CDRL3	CDRL3 SEQ ID	ELISA specificity
031S-A01	hFzd1ext	QASEDISNYLH	2122	GASTLQS	2816	CQQSYSPPWTF	3510	hFzd1L,2L,7L
032S-A01	hFzd1L	RASQGIGNSLA	2123	RASSLES	2817	CQQAHSFPPTF	3511	hFzd1L, mFzd1L
033S-A01	hFzd1L	RSSQSLLHSNGYNYLD	2124	LGSKRAS	2818	CMQALQTPLTF	3512	hFzd1L, mFzd1L
033S-B01	hFzd1L	RSSQSLLHSNGYNYLD	2125	GASSLQN	2819	CMQALQTPLTF	3513	hFzd1L, mFzd1L
033S-C01	hFzd1L	RSSQSLLHSNGYNYLD	2126	LGSSRAS	2820	CMQALQTPLTF	3514	hFzd1L, mFzd1L
033S-E01	hFzd1L	RSSQSLLHSNGYNYLD	2127	LGSNRAS	2821	CMQALQTPLIF	3515	hFzd1L, mFzd1L
033S-F01	hFzd1L	RSSQSLLHSNGYNYLD	2128	MGSNRAS	2822	CMQALQTPLTF	3516	hFzd1L, mFzd1L
033S-G01	hFzd1L	RSSQSLLHSNGYNYLD	2129	LGSNRAS	2823	CMQSLQTPLTF	3517	mFzd1L
033S-H01	hFzd1L	RSSQSLLHSNGYNYLD	2130	LGSNRAS	2824	CMQALQTPITF	3518	hFzd1L, mFzd1L
033S-B02	hFzd1L	RSSQSLLHSNGYNYLD	2131	LGSNRAS	2825	CMQTLQAPLTF	3519	hFzd1L, mFzd1L
033S-C02	hFzd1L	RSSQSLLHSNGYNYLD	2132	LGSNRAS	2826	CMQALQTPLTF	3520	hFzd1L, mFzd1L
033S-D02	hFzd1L	RSSQSLLHSNGYNYLD	2133	LGSHRAS	2827	CMQGLQTPITF	3521	hFzd1L, mFzd1L
033S-E02	hFzd1L	RSSQSLLHSNGYNYLD	2134	LGSNRAS	2828	CMQALQTPLTF	3522	hFzd1L, mFzd1L
033S-F02	hFzd1L	RSSQSLLHSNGYNYLD	2135	FGSNRAS	2829	CMQALQTPLTF	3523	hFzd1L, mFzd1L
033S-G02	hFzd1L	RSSQSLLHSNGYNYLD	2136	QGSNRAS	2830	CMQALQTPLTF	3524	hFzd1L, mFzd1L
033S-H02	hFzd1L	QASQDIRNYLN	2137	DASNLET	2831	CQQSYSVPYTF	3525	hFzd1L, mFzd1L
033S-A03	hFzd1L	RSSQSLLHSNGYNYLD	2138	AASTLQT	2832	CMQALQTPITF	3526	hFzd1L, mFzd1L
033S-B03	hFzd1L	RSSQSLLHSNGYNYLD	2139	LGSIRAS	2833	CMQALQTPLTF	3527	hFzd1L, mFzd1L
034S-C01	hFzd1L	RSSESLLHRNGYNYLD	2140	LGSNRAS	2834	CMQALQTPLTF	3528	hFzd1L, mFzd1L
033S-E03	hFzd1L	RSSQSLLHSNGYNYLD	2141	LGSNRAS	2835	CMQALQTPLTF	3529	hFzd1L, mFzd1L
034S-E01	hFzd1L	RSSQSLLHSNGYNYLD	2142	LGSNRAA	2836	CMQALQTPLTF	3530	hFzd1L, mFzd1L
034S-F01	hFzd1L	RSSQSLLHSNGYNYLD	2143	LGSHRAS	2837	CMQGLQTPLTF	3531	hFzd1L, mFzd1L

034S-H01	hFzd1L	RSSQSLLHSNGYNYLD	2144	LGSNRAS	2838	CMQALQTPLTF	3532	hFzd1L, mFzd1L
034S-A02	hFzd1L	RSSQSLLHSNGYNYLD	2145	LGSNRAS	2839	CMQGLQTPITF	3533	hFzd1L, mFzd1L
034S-B02	hFzd1L	RSSQSLLHSNGYNYLD	2146	LGSNRAS	2840	CMQTLRTPLTF	3534	hFzd1L, mFzd1L
034S-C02	hFzd1L	RSSQSLLHSNGYNYLD	2147	LGSNRAS	2841	CMQALQNPLTF	3535	hFzd1L, mFzd1L
034S-E02	hFzd1L	RSSZSLLHSNGYNYLD	2148	LGSNRAS	2842	CMQALQTPLTF	3536	hFzd1L
034S-F02	hFzd1L	RSSQSLLHSNGYNYLD	2149	AASSLQS	2843	CMQALQTPLTF	3537	hFzd1L
037S-D01	hFzd1L	RSSQSLLHSNGYNYLD	2150	MGSNRAS	2844	CMQALQTPLTF	3538	hFzd1L
037S-E01	hFzd1L	RSSQSLLNNNGNTYID	2151	LGSNRAS	2845	CMQTLKTPLSF	3539	hFzd1L
037S-F01	hFzd1L	QASQSIYNYLN	2152	GASSLHS	2846	CQQAISFPLTF	3540	hFzd1L
037S-G01	hFzd1L	RASQSISSWLA	2153	KASTLQS	2847	CQQSYSFPYTF	3541	hFzd1L
037S-H01	hFzd1L	RSSQSLLHSNGYNYLD	2154	LASNRAS	2848	CMQALQTPITF	3542	hFzd1L
037S-A02	hFzd1L	QASQDISNDLN	2155	AASTLHS	2849	CQQTYSTPYTF	3543	hFzd1L
037S-B02	hFzd1L	RASQSINKWLA	2156	AASSLQS	2850	CQQGYTTPLTF	3544	hFzd1L
032S-E01	mFzd1L	RSSQSLLHSNGYNYLD	2157	LASNRAS	2851	CMQAVQVPITF	3545	hFzd1L, mFzd1L
032S-E01	mFzd1L	QASQDISNYLN	2158	AAAILQN	2852	CQQSYSTPLTF	3546	hFzd1L, mFzd1L
032S-F01	mFzd1L	QASQDIRNYLN	2159	GASNLQS	2853	CQQSYNTPFTF	3547	mFzd1L
032S-C02	mFzd1L	RSSQSLLHSNGYNYLD	2160	AASRLQS	2854	CMQGTHWPLTF	3548	mFzd1L
032S-E02	mFzd1L	RASQDISNYLN	2161	GATTLMS	2855	CQQSYSTPFTF	3549	mFzd1L
032S-G02	mFzd1L	RASQDISNYLN	2162	GATTLMS	2856	CQQSYSTPFTF	3550	mFzd1L
031S-D01	hFzd2ext	RASQGISNNLN	2163	AASSLQS	2857	CQQSYRTPLTF	3551	hFzd1L,2L,7L
031S-E01	hFzd2ext	RSSQTINZYLN	2164	AASSLZS	2858	CQQANSFPLTF	3552	hFzd1L,2L,7L
031S-F01	hFzd2ext	RASQSVSSYVN	2165	KASSLER	2859	CQQSYSPPLTF	3553	hFzd2L
031S-G01	hFzd2ext	RSSQSLLHSNGYNYLD	2166	LGSNRAS	2860	CMQALQTPLTF	3554	hFzd2L
031S-B02	hFzd2ext	RASQSVSGSYLA	2167	GASTRAT	2861	CQQYGSSPLTF	3555	hFzd2L
034S-H02	hFzd2L	RASQGISSWLA	2168	DATNLAT	2862	CQQTYSTPYTF	3556	hFzd2L
034S-F03	hFzd2L	RSSQSLLHSNGYNYLD	2169	AASSLQS	2863	CMQALQTPYTF	3557	hFzd2L
034S-C09	hFzd2L	RASERISQYLN	2170	AASSLQS	2864	CQQSHRLPWTF	3558	hFzd2L, mFzd2L
034S-D09	hFzd2L	ZZZQSVZGNYLZ	2171	GASTRAT	2865	CQQYHSYPLTF	3559	hFzd2L, mFzd2L
034S-E09	hFzd2L	RASQSVSSSYLZ	2172	GASTRAT	2866	CQQYGSSPLTF	3560	hFzd2L, mFzd2L
034S-F09	hFzd2L	RASQSVSSSYLA	2173	GASTRAT	2867	CQQYGSSPLTF	3561	hFzd2L, mFzd2L
034S-A10	hFzd2L	RSSQSLLHSNGYNYLD	2174	LGSNRAS	2868	CMQSLQNPITF	3562	hFzd2L, mFzd2L
034S-D10	hFzd2L	RSSQSLLHSNGYNYLD	2175	AASTLQS	2869	CMQGLQTPITF	3563	hFzd2L, mFzd2L
034S-C11	hFzd2L	RSSQSLLHSNGYNYLD	2176	AASSLQS	2870	CMQALQTPITF	3564	hFzd2L, mFzd2L
034S-C12	hFzd2L	RSSQSLLHSNGYNYLD	2177	LGSNRAS	2871	CMQALQTPITF	3565	mFzd2L
034S-F12	hFzd2L	RSSQSLLHSNGYNYLD	2178	KASSLEN	2872	CMQGSHWPPTF	3566	mFzd2L
034S-G12	hFzd2L	RSSQSZZHSNGYNYLD	2179	LGSNRAS	2873	CMQSLQNPITF	3567	mFzd2L
035S-D01	hFzd2L	RASQSVSSNYLA	2180	GASTRAT	2874	CQQYHSYPLTF	3568	mFzd2L

036S-A01	hFzd2L							hFzd2L, mFzd2L
037S-C02	hFzd2L	RASERISQYLN	2181	AASSLQS	2875	CQQSHRLPWTF	3569	hFzd2L
037S-G02	hFzd2L	RASQRVNTNYLA	2182	GASTRAT	2876	CQQYATSPLTF	3570	hFzd2L
037S-A03	hFzd2L	RZZQSLPPSNGY NYLD	2183	AASSLQS	2877	CMQATHWPYTF	3571	hFzd2L
037S-C03	hFzd2L	RSSQSLLYSNGYT YVD	2184	LGSNRAS	2878	CMQALQTPITF	3572	hFzd2L
037S-D03	hFzd2L	QASQDIRTDLH	2185	ATSSLQS	2879	CQQANSFPFTF	3573	hFzd2L
037S-E03	hFzd2L	RASERISQYLN	2186	AASSLQS	2880	CQQSHRLPWTF	3574	hFzd2L
037S-H03	hFzd2L	RSSQSLLHSNGY TYLD	2187	VASNWAS	2881	CMQALQTPLSF	3575	hFzd2L
037S-B04	hFzd2L	RSSQSLLYTNGLT YVD	2188	LGSNRAS	2882	CMQALQTPITF	3576	hFzd2L
037S-F04	hFzd2L							hFzd2L
037S-H04	hFzd2L	RSSQSLLHSNGY NYLD	2189	AASTLQS	2883	CMQSIQLPLTF	3577	hFzd2L, mFzd2L
037S-F05	hFzd2L	RASQDIKNDLG	2190	AASSLQS	2884	CLQSFSSPWTF	3578	hFzd2L
048S-E01	hFzd2L	RSSQSLLFTNGH NYLD	2191	LGSSRAS	2885	CMQALQTPLTF	3579	hFzd2L
048S-C01	hFzd2L	RSSQSLLHSNGY NYLD	2192	LGSNRAS	2886	CMQGTHWPPTF	3580	hFzd2L
048S-G01	hFzd2L	RSSQSLZHSNGY KYLD	2193	LGSHRPS	2887	CMQALQTPITF	3581	hFzd2L
048S-D01	hFzd2L	RSSQSLLHSNGY NYLD	2194	LGSHRAS	2888	CMQALQTPITF	3582	hFzd2L
048S-B02	hFzd2L	RASERISQYLN	2195	AASSLQS	2889	CQQSHRLPWTF	3583	hFzd2L
048S-F01	hFzd2L	RSSQSLLHSNGY NYLD	2196	LGSNRAS	2890	CMQALQTPLTF	3584	hFzd2L
048S-H01	hFzd2L	RASQSVSSSYLA	2197	GASTRAT	2891	CQQYYSNPLTF	3585	hFzd2L
048S-A02	hFzd2L	RASQGISSYLN	2198	GSTNLQN	2892	CQQVNSLPITF	3586	hFzd2L
048S-C02	hFzd2L	RSSQSLLHSNGY NYLD	2199	LGSNRAS	2893	CMQALETPLTF	3587	hFzd2L
048S-E02	hFzd2L	KSSQSVLYSSNN KNYLA	2200	WASTRES	2894	CHQYYSTPLTF	3588	hFzd2L
048S-A01	hFzd2L	RSSQSLLHSNGY NYLD	2201	AASSLQS	2895	CMQALQTPYTF	3589	hFzd2L, mFzd2L
049S-A01	hFzd2L	RASQSVSSSYLA	2202	GASTRAT	2896	CQQYGSSPLTF	3590	hFzd2L, mFzd2L
049S-C01	hFzd2L	RSSQSLLHSNGY NYLD	2203	LGSNRAS	2897	CMQALEIPVTF	3591	hFzd2L, mFzd2L
049S-D01	hFzd2L	RASQGISNYLN	2204	AASSLQS	2898	CQQSYFTPLTF	3592	hFzd2L, mFzd2L
049S-E01	hFzd2L	RSSQSLLHSNGY NYLD	2205	LGSNRAS	2899	CMQSLQNPITF	3593	hFzd2L, mFzd2L
044S-G10	mFzd3L	RASQSISSYLN	2206	AASTLQG	2900	CQQSYSVPITF	3594	hFzd3L, hFzd6L
044S-H10	mFzd3L	RASQTITSNYLA	2207	GASTRAT	2901	CQQYGSLPIAF	3595	mFzd3L
044S-A11	mFzd3L	RASQSISSYLN	2208	KASSLES	2902	CQQTNSFPITF	3596	mFzd3L
044S-B11	mFzd3L	RSSQSLLHSNGY NYLD	2209	LSSNRAS	2903	CMQALQTPITF	3597	hFzd3L, mFzd3L
044S-C11	mFzd3L	RSSQSLLHSNGY NYLD	2210	YASQSIS	2904	CMQATQFPWTF	3598	hFzd3L, hFzd6L
044S-E11	mFzd3L	KSSQSVLYTSNN KNYLA	2211	ZASTRES	2905	CQQYYRTPITF	3599	hFzd3L, hFzd6L
044S-F11	mFzd3L	QASQNZZTFLN	2212	DASNLET	2906	CQQSYSTPLTF	3600	hFzd3L, mFzd3L
044S-G11	mFzd3L	QASQDISNYLN	2213	DASNLET	2907	CQQTYSSPWTF	3601	hFzd3L, mFzd3L
044S-H11	mFzd3L	RASQNIDKWLA	2214	AASZZQS	2908	CQQSYNTPFTF	3602	hFzd3L, mFzd3L

044S-B12	mFzd3L	RASQGISNYLA	2215	AASSLQS	2909	CQQSYSTPLTF	3603	hFzd3L, mFzd3L
044S-C12	mFzd3L	RASQTVGTTYLA	2216	AASSRAA	2910	CQQRSNWPPSITF	3604	hFzd3L, mFzd3L
044S-D12	mFzd3L	RSSQSLLHSNGYNYLD	2217	LGSNRAS	2911	CMQGSHWPLTF	3605	hFzd3L, hFzd6L
044S-E12	mFzd3L	RASQRIGTYLN	2218	ATSSLHT	2912	CQQSYSTPFTF	3606	hFzd3L, mFzd3L
044S-F12	mFzd3L	KSSQSVLYSSNNKNYLA	2219	WASTRES	2913	CQQYYSSPITF	3607	hFzd3L, hFzd6L
045S-A01	mFzd3L	RASQGISSWLA	2220	AASSLQS	2914	CQQSYSPPYTF	3608	hFzd3L, mFzd3L
045S-B01	mFzd3L	QASQDIRKYLN	2221	AASTLQS	2915	CQQSYSTPPTF	3609	hFzd3L, hFzd6L
045S-C01	mFzd3L	RASQSISRYLH	2222	GASNLET	2916	CQQANTSPITF	3610	hFzd3L, mFzd3L
045S-D01	mFzd3L	RSSQSLLHSNGYNYLD	2223	AASSLQS	2917	CMQGAHWPPTF	3611	hFzd3L, mFzd3L
045S-E01	mFzd3L	KSSQSVLYSSNNKNYLA	2224	WASTRES	2918	CQQYFSSPITF	3612	hFzd3L, mFzd3L
045S-G01	mFzd3L	RASQSISSHLN	2225	AASTLQS	2919	CQQSYSTPLTF	3613	hFzd3L, mFzd3L
045S-H01	mFzd3L	RASQSISSYLN	2226	AASSLHS	2920	CQQANSFPITF	3614	hFzd3L, mFzd3L
045S-A02	mFzd3L	QASQDINNYLN	2227	AASTLQS	2921	CQQSYTTPITF	3615	hFzd3L, mFzd3L
045S-B02	mFzd3L	RASQNIKRYLN	2228	AASSLQS	2922	CQQSHSSPVTF	3616	hFzd3L, mFzd3L
045S-D02	mFzd3L	RASQSISNNLN	2229	ASSRLQT	2923	CQQSYTIPITF	3617	hFzd3L, mFzd3L
045S-E02	mFzd3L	RASQSIGSYLN	2230	AASSLQS	2924	CQQANSFPLSF	3618	hFzd3L, mFzd3L
045S-F02	mFzd3L	QASQDISNYLN	2231	DASNLET	2925	CQQSFSIPLTF	3619	hFzd3L, mFzd3L
045S-G02	mFzd3L	KSSQSVFYNSNNKNYLA	2232	WASTRAY	2926	CQQFYSTPITF	3620	hFzd3L, mFzd3L
045S-H02	mFzd3L	RASQGIGNYLA	2233	AASSLQS	2927	CQQSYSTPFTF	3621	hFzd3L, mFzd3L
045S-A03	mFzd3L	RSSQSLLHSNGYNYLD	2234	LGSNRAS	2928	CMQSLQAPITF	3622	hFzd3L, mFzd3L
045S-B03	mFzd3L	RSSQSLLHSNGYNYVD	2235	LGSNRAS	2929	CMQGTHWPITF	3623	hFzd3L, mFzd3L
045S-C03	mFzd3L	RASQSISSYLN	2236	AASSLQS	2930	CQQSYSTPLTF	3624	hFzd3L, mFzd3L
045S-D03	mFzd3L	QASQDISNYLN	2237	AASNLQS	2931	CQQTYRNPITF	3625	hFzd3L, mFzd3L
045S-F03	mFzd3L	RASQAINSYLA	2238	DATNLKT	2932	CQQSYSTPLTF	3626	hFzd3L, mFzd3L
045S-G03	mFzd3L	RSSQSLLHSNGYNYLD	2239	LGSNRAS	2933	CMQALQTPLTF	3627	hFzd3L, mFzd3L
045S-H03	mFzd3L	KSSQSVLYSSNNKNYLA	2240	WASTRQS	2934	CQQYYGSPITF	3628	hFzd3L, mFzd3L
045S-A04	mFzd3L	RASQGISNYLA	2241	GASSLQG	2935	CQQSYRTVTF	3629	hFzd3L, hFzd6L
045S-B04	mFzd3L	RASQSISSYLN	2242	KASSLES	2936	CQQANSFPLTF	3630	hFzd3L, mFzd3L
045S-D04	mFzd3L	RSSQSLLHSNGYNYLD	2243	AASNLQS	2937	CMQGLQTPWTF	3631	hFzd3L, mFzd3L
045S-E04	mFzd3L	RASQGIRNDLG	2244	AASSLQS	2938	CQQSYSTPYTF	3632	hFzd3L, mFzd3L
045S-F04	mFzd3L	RASQHINRYLN	2245	GASNLET	2939	CQQSYSYPITF	3633	hFzd3L, mFzd3L
045S-G04	mFzd3L	RASQGISSWLA	2246	AASTLQS	2940	CQQTWGPPFTF	3634	hFzd3L, mFzd3L
045S-H04	mFzd3L	RSSQSLLHSNGYNYLD	2247	LGSNRAS	2941	CMQALQTPITF	3635	hFzd3L, mFzd3L
045S-A05	mFzd3L	QASQDISNYLN	2248	AASTLQS	2942	CQQTYATPPTF	3636	hFzd3L, mFzd3L

045S-B05	mFzd3L	RSSQSLLHSNGYNYLD	2249	LGSNRAS	2943	CMQALQTPLTF	3637	hFzd3L, mFzd3L
045S-C05	mFzd3L	RASQTISDYLN	2250	KASTLGS	2944	CQQANTFPYTF	3638	hFzd3L, mFzd3L
045S-D05	mFzd3L	RSSQSLLHSNGYNYLD	2251	LGSNRAS	2945	CMQALQTPLTF	3639	hFzd3L, mFzd3L
045S-E05	mFzd3L	RASQGIRSDLG	2252	KASSLES	2946	CQQSYTIPITF	3640	hFzd3L, mFzd3L
045S-F05	mFzd3L	RSSQSLLHSNGYNYLD	2253	AASSLQS	2947	CMQALQTPYTF	3641	hFzd3L, mFzd3L
045S-G05	mFzd3L	RASQSISSYLN	2254	DASNLET	2948	CQQSLSTPITF	3642	hFzd3L, mFzd3L
045S-A06	mFzd3L	RASLSVTNNYLA	2255	GASTRAT	2949	CHQYGNFPLTF	3643	hFzd3L, mFzd3L
045S-B06	mFzd3L	RSSQSLLHSNGYNYLD	2256	AASSLQS	2950	CMQGTQWPLTF	3644	hFzd3L, mFzd3L
045S-C06	mFzd3L	RASQGISSYLA	2257	AASSLQS	2951	CQQSYSTPLTF	3645	hFzd3L, mFzd3L
045S-D06	mFzd3L	RASQSISSYLN	2258	AASSLQS	2952	CQQSYSTPLTF	3646	hFzd3L, mFzd3L
045S-E06	mFzd3L	RASQSISSYLN	2259	AASSLQS	2953	CQQSYSTPLTF	3647	hFzd3L, mFzd3L
045S-G06	mFzd3L	QASQDISNYLN	2260	SASTLQS	2954	CQQTYSIPITF	3648	hFzd3L, mFzd3L
045S-H06	mFzd3L	RASQSISSYLN	2261	AASSLQS	2955	CQQSYTTPITF	3649	hFzd3L, mFzd3L
045S-A07	mFzd3L	RASQDISNYLN	2262	AASILQS	2956	CQQTYSIPITF	3650	mFzd3L
045S-C07	mFzd3L	RASQGISNYLA	2263	QASTSQS	2957	CQQSDSPPFTF	3651	hFzd3L, mFzd3L
044S-D01	hFzd3L	RASQSISKWLA	2264	GASTLQA	2958	CQQYNSYWTF	3652	hFzd3L, mFzd3L
044S-E01	hFzd3L	KSSQSVLYSSNNKNYLA	2265	WASTRES	2959	CQQYYSTPWTF	3653	hFzd3L, mFzd3L
044S-F01	hFzd3L	RASQSISSYLN	2266	NASSLQS	2960	CQQGYSAPFTF	3654	hFzd3L, mFzd3L
044S-G01	hFzd3L	QASQGINNYLN	2267	DASTLES	2961	CQQAKSFPLTF	3655	hFzd3L, mFzd3L
044S-A02	hFzd3L	RASQNIGSYLN	2268	AASSLQT	2962	CQQSYSPPLTF	3656	hFzd3L, mFzd3L
044S-B02	hFzd3L	RASQNIGSWLA	2269	AASSLQS	2963	CQQSYSTPLTF	3657	hFzd3L, mFzd3L
044S-C02	hFzd3L	QASQDISNYLN	2270	DASNLET	2964	CQRADSFPLTF	3658	hFzd3L, mFzd3L
044S-D02	hFzd3L	RSSQSLLHSNGYNYLD	2271	LGSNRAS	2965	CKQALQTPITF	3659	hFzd3L, mFzd3L
044S-E02	hFzd3L	RSSQSLLHSNGYNYLD	2272	AASSLQS	2966	CMQALQAPYTF	3660	hFzd3L, mFzd3L
044S-F02	hFzd3L	RSSQSLLHSNGYNYLD	2273	LGSNRAS	2967	CMQSLQTPLTF	3661	hFzd3L, mFzd3L
044S-H02	hFzd3L	RASQSISRWLA	2274	KASSLES	2968	CQQYYNAPPTF	3662	hFzd3L, hFzd6L
044S-B03	hFzd3L	RASQGISNYLA	2275	KASSLES	2969	CQQNYSFPFTF	3663	hFzd3L, hFzd6L
044S-C03	hFzd3L	RASQSVSSSYLA	2276	GASTRAT	2970	CQQYGHLPVSF	3664	hFzd3L, hFzd6L
044S-D03	hFzd3L	RASQYISNYLN	2277	AASSLQS	2971	CQQSYSAPYTF	3665	hFzd3L, mFzd3L
044S-E03	hFzd3L	RASQDISNYLN	2278	AASNLET	2972	CQQANSFPLTF	3666	hFzd3L, mFzd3L
044S-F03	hFzd3L	RSSQSLLHSNGYNYLD	2279	LGSNRAS	2973	CMQGTHLPPTF	3667	hFzd3L, hFzd6L
044S-G03	hFzd3L	RASQSISRWLA	2280	TASTLQS	2974	CQQANSFPPTF	3668	hFzd3L, mFzd3L
044S-A04	hFzd3L	RASQSISTYLN	2281	TASNLQT	2975	CQQTYSLPWTF	3669	hFzd3L, mFzd3L
044S-C04	hFzd3L	RASQNINSYLH	2282	AASHLQS	2976	CQQANTFPITF	3670	hFzd3L, hFzd6L

044S-D04	hFzd3L	RSSQSLLHSNGYNYLD	2283	LGSSRAS	2977	CMQALQTPFTF	3671	hFzd3L, hFzd6L
044S-A01	hFzd3L	RASQDISNYLN	2284	QASTLER	2978	CQQSYSTPFTF	3672	hFzd3L
044S-B01	hFzd3L	RASQDIRSDLG	2285	AASTLQS	2979	CQQANSFPSF	3673	mFzd3L
044S-C01	hFzd3L	RASQYISNYLN	2286	AASTLQS	2980	CQQADRLPLTF	3674	mFzd3L
044S-G02	hFzd3L	RASQSISRWLA	2287	TASTLQS	2981	CQQANSFPPTF	3675	hFzd3L, mFzd3L
044S-H03	hFzd3L	KSSQSVLYSSNNKNYLA	2288	WASTRES	2982	CQQYYSSPLTF	3676	mFzd3L
044S-B04	hFzd3L	QASQDISNYLN	2289	RASSLQS	2983	CQQANSFPPTF	3677	mFzd3L
044S-G04	hFzd3L	QASQDISNYLN	2290	AASTLQS	2984	CQQTNSFPPTF	3678	mFzd3L
044S-H04	hFzd3L	RASQSINNWLA	2291	DASNLQT	2985	CQQRYSTPLTF	3679	hFzd3L, mFzd3L
044S-A05	hFzd3L	RASQSISSYLN	2292	AASSLQS	2986	CQQSYSTPLTF	3680	hFzd3L, mFzd3L
044S-B05	hFzd3L	RASQSIZSYLN	2293	AASTLRS	2987	CQQSYSTPPTF	3681	mFzd3L
044S-C05	hFzd3L	RASQSISSYLN	2294	TASSLQS	2988	CQQSYSVPLTF	3682	hFzd3L, mFzd3L
044S-D05	hFzd3L	KSSRSVLNSSNNKNYLA	2295	WASTRAS	2989	CQQYYSSPYTF	3683	hFzd3L, hFzd6L
044S-E05	hFzd3L	RSSQSLLHSNGYNYLD	2296	SGSSRAS	2990	CMQALQTPITF	3684	hFzd3L, mFzd3L
044S-G05	hFzd3L	RASQSISVYLN	2297	DASKLQS	2991	CQQSFNTPWTF	3685	hFzd3L, hFzd6L
044S-H05	hFzd3L	RASQSISSYLN	2298	AASSLQS	2992	CQQSYSTPLTF	3686	hFzd3L, mFzd3L
044S-A06	hFzd3L	RSSQSLLHSNGYNYLD	2299	LGSNRAS	2993	CMQSTHWPPTF	3687	hFzd3L, mFzd3L
044S-B06	hFzd3L	RASQSINRYLN	2300	GASSLQS	2994	CQQTNSFPFTF	3688	hFzd3L, mFzd3L
044S-C06	hFzd3L	RASQSISRHLT	2301	AASSLHT	2995	CQQSYSTPYTF	3689	hFzd3L, mFzd3L
044S-D06	hFzd3L	RASQSISTYLN	2302	SASNLQS	2996	CQQSDSPPVTF	3690	hFzd3L, mFzd3L
044S-E06	hFzd3L	RASQGIGTWLA	2303	AASTLQS	2997	CQQSYSTPFTF	3691	hFzd3L, mFzd3L
044S-F06	hFzd3L	RASQSINKWLA	2304	AASTLQS	2998	CQQANSLPFTF	3692	hFzd3L, mFzd3L
044S-G06	hFzd3L	RSSQSLLHSNGYNYLD	2305	LGSYRAS	2999	CMQALQTPTF	3693	hFzd3L, mFzd3L
044S-H06	hFzd3L	KSSQSVLYSSNNKNYLA	2306	WASTRES	3000	CQQYYTTPITF	3694	hFzd3L, mFzd3L
044S-A07	hFzd3L	KSSQSVLYRSNNKNYLA	2307	WASTRES	3001	CQQYFSVPFTF	3695	hFzd3L, mFzd3L
044S-B07	hFzd3L	QASQDISNYLN	2308	KASSLES	3002	CQQSYSTPITF	3696	hFzd3L, mFzd3L
044S-C07	hFzd3L	QASQDISNYLN	2309	AASTLQS	3003	CQQANSFPITF	3697	hFzd3L, mFzd3L
044S-D07	hFzd3L	RSSQSLLHSNGYNYLD	2310	LGSNRAS	3004	CMQALQAPTF	3698	hFzd3L, mFzd3L
044S-E07	hFzd3L	RSSQSLLHSNGYNYLD	2311	AASSLQS	3005	CMQALQTPITF	3699	hFzd3L, mFzd3L
044S-F07	hFzd3L	QASQDITNYLN	2312	KASSLES	3006	CQQANSFPVTF	3700	hFzd3L, mFzd3L
044S-G07	hFzd3L	RSSQSLLHZZZYNYLD	2313	AASALQS	3007	CMQARQTPITF	3701	mFzd3L
044S-H07	hFzd3L	RASQNISNYLN	2314	KASSLES	3008	CQESYTTPFTF	3702	hFzd3L, mFzd3L
044S-A08	hFzd3L	RSSQSLLHSNGYNYLD	2315	LGSNRAS	3009	CMQALQTPLTF	3703	hFzd3L, mFzd3L
044S-B08	hFzd3L	RASQSVSRWLA	2316	DASNLET	3010	CQQTYNPPLTF	3704	mFzd3L
044S-C08	hFzd3L	RSSQSLLHSNGYNYLD	2317	LGSNRAS	3011	CMQALQNPLTF	3705	hFzd3L, mFzd3L
044S-E08	hFzd3L	RASQTIDNYLQ	2318	AASSLQS	3012	CQQSYITPYTF	3706	hFzd3L, mFzd3L

044S-F08	hFzd3L	RASQSVSSSYLS	2319	ATSSRAA	3013	CQQRSNWPPTITF	3707	hFzd3L, mFzd3L
044S-G08	hFzd3L	RASQSISNWLA	2320	AASILQR	3014	CQQSYSPPTTF	3708	hFzd3L, mFzd3L
044S-A09	hFzd3L	RASQSISSYLN	2321	KASTLES	3015	CQQSYKSPLTF	3709	hFzd3L, mFzd3L
044S-B09	hFzd3L	RSSQSLLHSNGYNYLD	2322	LGSNRAS	3016	CMQGLQTPTF	3710	hFzd3L, mFzd3L
044S-C09	hFzd3L	RASQAIRNDLG	2323	AASSLQS	3017	CQQGYNPPRTF	3711	hFzd3L, mFzd3L
044S-E09	hFzd3L	RASQGISNYLA	2324	DASNLET	3018	CQQSYSPPYTF	3712	hFzd3L, mFzd3L
044S-F09	hFzd3L	RVSQGISSYLN	2325	AASSLQS	3019	CQQSYTLPITF	3713	hFzd3L, hFzd6L
044S-G09	hFzd3L	RASQSISSYLN	2326	GASTLQS	3020	CQQSYSTPFTF	3714	hFzd3L, mFzd3L
044S-H09	hFzd3L	RASQSISSYLN	2327	RASSLQG	3021	CQQSYSTPYTF	3715	hFzd3L, hFzd6L
044S-A10	hFzd3L	RSSQSLLHSNGYNYLD	2328	LGSYRAS	3022	CMQGTHWPPAF	3716	hFzd3L, mFzd3L
044S-B10	hFzd3L	RASQSISTWLA	2329	AASSLQS	3023	CQQSYNTPITF	3717	hFzd3L, mFzd3L
044S-D10	hFzd3L	RASQSVSSNLA	2330	GASTRAT	3024	CQQYKSYPLTF	3718	hFzd3L, mFzd3L
038S-B01	hFzd4L	RSSQSLZHSNGYNYLD	2331	LGSHRAS	3025	CMQAIQIPYSF	3719	hFzd4L
038S-D01	hFzd4L	RASZSIZSWLA	2332	AASSLQS	3026	CQQANSFPLTF	3720	hFzd4L
038S-D03	hFzd4L	RASQGIGNFLA	2333	AASSLQS	3027	CQQANSFPLTF	3721	hFzd4L
038S-E02	hFzd4L	RASQGISSWLA	2334	GSSRLPS	3028	CQQSYNIPLTF	3722	hFzd4L
038S-E03	hFzd4L	RSSQSLLHSNGYNYLD	2335	LGSNRAS	3029	CMQALRTPVTF	3723	hFzd4L
038S-E05	hFzd4L	RSSRSLLYTNGLTYID	2336	LGSNRAS	3030	CMQALQTPLTF	3724	hFzd4L
038S-A04	hFzd4L	RSSQSLLHSNGYNYLD	2337	LGSNRAS	3031	CMQGLQTPVTF	3725	hFzd4L
038S-D04	hFzd4L	RSIQSLLHSNGYKYLD	2338	TASTLQT	3032	CKQANQTPITF	3726	hFzd4L
038S-E01	hFzd4L	RSSQSRASQNIZNYLA	2339	VASNLES	3033	CKQGDQIPPTF	3727	hFzd4L
038S-C08	hFzd4L	RASQSISTWLA	2340	GASVLQS	3034	CQQSYSTPLTF	3728	hFzd4L
038S-A03	hFzd4L	RASQGISNYLA	2341	DASSLQG	3035	CQQSYSEVLTF	3729	hFzd4L
039S-B03	hFzd4L	RASQDIGNELG	2342	AASNLQA	3036	CQQSYTAPLTF	3730	hFzd4L
038S-B02	hFzd4L	QASQDISNYLN	2343	AASTLQS	3037	CQQSHSLPYTF	3731	hFzd4L
038S-G03	hFzd4L	RASQGIGNFLA	2344	AASNWQS	3038	CQQANSFPFTF	3732	hFzd4L
039S-B06	hFzd4L	RASQDIRTNLA	2345	AASSLQS	3039	CQQSYSLPWTF	3733	hFzd4L
038S-C02	hFzd4L	RASQNINTYLN	2346	AASSLQS	3040	CQQYDSYPLTF	3734	hFzd4L
039S-B02	hFzd4L	RSSRSLLHKNGHTYVE	2347	LGSNRAS	3041	CMQSLQTPLTF	3735	hFzd4L
038S-B04	hFzd4L	RASQSISSRLA	2348	SASNLET	3042	CQQTYHTPWTF	3736	hFzd4L
039S-G02	hFzd4L	QASQDISNYLN	2349	AASTLQT	3043	CQQSYSTPWTF	3737	hFzd4L
039S-F04	hFzd4L	RSSQSLLHSNGYNYLD	2350	AASSLQS	3044	CMQGLQTPHTF	3738	hFzd4L
038S-B08	hFzd4L	RSSQSLLHSNGYNYLD	2351	TASTLZS	3045	CMQGLQTPHTF	3739	hFzd4L
038S-C10	hFzd4L	RASQGINNYLA	2352	GASNLET	3046	CQQSNTFPLTF	3740	hFzd4L
038S-F06	hFzd4L	YTFSSYYMH	2353	GWZNPNGGNTZYA	3047	CARDGSLDYW	3741	hFzd4L
038S-F07	hFzd4L	RASQDIRNYLA	2354	AASSLQS	3048	CQQAYSSPLTF	3742	hFzd4L
038S-H06	hFzd4L	RSSQSLLHSNGYNYLD	2355	AASTLQS	3049	CMQALQTPYTF	3743	hFzd4L

038S-G07	hFzd4L	RASZDIRNYLA	2356	AASSLQS	3050	CQQAYSSPLTF	3744	hFzd4L
038S-F12	hFzd4L	RSSQSLLHSNGY NYLD	2357	LGSNRAS	3051	CMQGLQTPHTF	3745	hFzd4L
038S-B07	hFzd4L	KSSRSVLYSSNKK NYLA	2358	ZZSTRES	3052	CQQYYSSPLTF	3746	hFzd4L
039S-B04	hFzd4L	RASQGISSSLA	2359	AASNLQS	3053	CQQSYSTPWTF	3747	hFzd4L
039S-C02	hFzd4L	RASQGISNNLN	2360	RASILQS	3054	CQQSYSTPLTF	3748	hFzd4L
039S-H05	hFzd4L	RSSQSLLHSNGY NYLD	2361	LGSNRAS	3055	CMQALQTPLTF	3749	hFzd4L
039S-G01	hFzd4L	RASQSISTWLA	2362	AASSLQS	3056	CQQAKSFPYTF	3750	hFzd4L
039S-E03	hFzd4L	RSSQSLLHSNGY NYLD	2363	LGTNRAS	3057	CMQALQAPTTF	3751	hFzd4L
039S-C01	hFzd4L	RSSQSLLHSNGY NYLD	2364	AASSLQS	3058	CMQALQTPHTF	3752	hFzd4L
039S-F02	hFzd4L	RASQGISTWLS	2365	SASZLQS	3059	CQQANSFPLTF	3753	hFzd4L
039S-E04	hFzd4L	RSSQSLLHSNGY NYLD	2366	LASNRAS	3060	CMQALQTPYTF	3754	hFzd4L
039S-C05	hFzd4L	RASQSISSYLN	2367	AASSLQS	3061	CQQSYSTPLTF	3755	hFzd4L
039S-F06	hFzd4L	QASQSISTHLN	2368	AASSLQS	3062	CQQSFSIPWTF	3756	hFzd4L
039S-A07	hFzd4L	RASQSVGTWLA	2369	AASSLQS	3063	CQQSYSSPYTF	3757	hFzd4L
039S-E10	hFzd4L	RSSQSLLHSNGY NYLD	2370	LGSNRAS	3064	CRQALQIPYTF	3758	hFzd4L
039S-G07	hFzd4L	RSGRPIADYLS	2371	KASSLGS	3065	CQQAYSFPWTF	3759	hFzd4L
039S-A10	hFzd4L	RSSQSLLHSNGY NYLD	2372	AASSLQS	3066	CMQALQTPYTF	3760	hFzd4L
039S-B07	hFzd4L	RSSQSLLHSNGY NYLD	2373	LGSNRAS	3067	CMQALQTPATF	3761	hFzd4L
039S-B09	hFzd4L	RSSQSLLHSNGY NYLD	2374	LGSNRAS	3068	CMQALQTPHTF	3762	hFzd4L
039S-A08	hFzd4L	RZSQGIGNFLA	2375	AASSLQS	3069	CQQANSLPLTF	3763	hFzd4L
039S-C09	hFzd4L	RSSQSLLHSNGY NYLD	2376	AASSLQS	3070	CMQALQTPHTF	3764	hFzd4L
039S-E07	hFzd4L	RASQSISRWLA	2377	GASSLQR	3071	CQQADSFPYTF	3765	hFzd4L
039S-H09	hFzd4L	RSSQSLLHSNGY NYLD	2378	LGSNRAS	3072	CMQALQTPPTF	3766	hFzd4L
040S-B01	hFzd4L	RSSQSLLHSNGY NYLD	2379	LGSNRAS	3073	CMQALHTPNTF	3767	hFzd4L
040S-A02	hFzd4L	RSSQSLLHSNGY NYLD	2380	XGSNRAS	3074	CMQALQTPLTF	3768	hFzd4L
040S-H04	hFzd4L	KSSQSLLHSDGKT YLY	2381	KISNRFS	3075	CMQATQFPYTF	3769	hFzd4L
040S-E05	hFzd4L	RSSQSLLHSNGY NYLD	2382	LGSNRAS	3076	CMQALQTPRTF	3770	hFzd4L
039S-H10	hFzd4L	RSSQSLLHSNGY NYLD	2383	AASSLQS	3077	CMQALQTPYTF	3771	hFzd4L
040S-B02	hFzd4L	KSSRSVLYSSNKK NYLA	2384	WASTRES	3078	CQQYYSSPLTF	3772	hFzd4L
040S-C02	hFzd4L	RSSQSLLHSNGY NYLD	2385	LGSNRAS	3079	CMQALQTPYTF	3773	hFzd4L
040S-A05	hFzd4L	RSSRSLLYSNGYN YLD	2386	LZSHRAS	3080	CMQALQTPYTF	3774	hFzd4L
039S-C12	hFzd4L	RSSQSLLHSNGY NYLD	2387	LGSNRAS	3081	CMQALQTPITF	3775	hFzd4L
039S-F12	hFzd4L	RASQGIGNFLA	2388	AASSLQS	3082	CQQANSLPLTF	3776	hFzd4L
040S-E01	hFzd4L	RSSQSLLHSNGY NYLD	2389	LGSNRAS	3083	CMQALQTPPTF	3777	hFzd4L
040S-E02	hFzd4L	RSSQSLLHSNGY NYLD	2390	LGSHRAS	3084	CMQALQTPYSF	3778	hFzd4L
039S-F11	hFzd4L	RSSQSLLHSNGY NYLD	2391	AASSLQS	3085	CMQALQTPITF	3779	hFzd4L

040S-F01	hFzd4L	RSSQSLLHSNGYNYLD	2392	LGSNRAS	3086	CMQALQTPITF	3780	hFzd4L
040S-F02	hFzd4L	RASQGIRNDLG	2393	AASNLQS	3087	CQQSYSTPLTF	3781	hFzd4L
040S-E04	hFzd4L	RSSRSLLYSNGYNYLD	2394	LASHRAS	3088	CMQALQTPYTF	3782	hFzd4L
040S-D05	hFzd4L	TLHSGINVGTYRIY	2395	DKSDSDNHKGS	3089	CMIWHNNAWVF	3783	hFzd4L
039S-G11	hFzd4L	RASQSISSYLN	2396	KASNLEN	3090	CQQTYSMPLTF	3784	hFzd4L
040S-G01	hFzd4L	KSSQSLLYSSNNKNYLA	2397	GASTRYS	3091	CQQYYSTPVTF	3785	hFzd4L
036S-C01	hFzd5L	RASETISSWLA	2398	GASSLQS	3092	CQQYGSSPLTF	3786	hFzd5L
036S-F01	hFzd5L	RSSQSLLHSNGYNYLD	2399	LGSDRAS	3093	CMQGLQTPLTF	3787	hFzd5L, mFzd5L
036S-B02	hFzd5L	RSSQSLLHSNGYNYLD	2400	AASSLQS	3094	CMQGTHWPLTF	3788	hFzd5L
036S-D02	hFzd5L	RZSQSLLHSZGYNYLD	2401	AASNWQS	3095	CMQSFQTPFTF	3789	hFzd5L
036S-F02	hFzd5L	RSSQSLLHSNGYNYLD	2402	LGSNRAS	3096	CMQGLQTPLTF	3790	hFzd5L
036S-G02	hFzd5L	RSSQSLLHSNGYNYLD	2403	LGSNRAS	3097	CMQGLQTPLTF	3791	hFzd5L
036S-H02	hFzd5L	RSSQSLLHSNGYNYLD	2404	LGSDRAS	3098	CMQALQTPLTF	3792	hFzd5L
036S-A03	hFzd5L	RSSQSLLHSNGYNYLD	2405	LAZDRAS	3099	CMQVLQTPLTF	3793	hFzd5L
036S-C03	hFzd5L	RSSQSLLHSNGYNYLD	2406	LGSNRAS	3100	CMQGLQTPLTF	3794	hFzd5L
036S-C04	hFzd5L	RASQSISSSLN	2407	DASYLQS	3101	CQQGYSIPFTF	3795	hFzd5L
036S-D04	hFzd5L	RASETISSWLA	2408	GASSLQS	3102	CQQYGRSPLTF	3796	hFzd5L
036S-E04	hFzd5L	RSSQSLLHSNGYNYLD	2409	DGSNLET	3103	CMQGTQRPLTF	3797	hFzd5L
036S-A05	hFzd5L	RASQNIGPWLA	2410	DASNLET	3104	CQQSYSIPLTF	3798	hFzd5L, mFzd5L
036S-B05	hFzd5L	RSSQSLLHSNGYNYLD	2411	DASNLET	3105	CMQGTHWPWTF	3799	hFzd5L
036S-C05	hFzd5L	RSSQSLLHSNGYNYLD	2412	AASNLQS	3106	CMQVLQPPYTF	3800	hFzd5L
036S-D05	hFzd5L	RCSQSLLPSNGYNYLD	2413	LGSNRAS	3107	CMQGLQTPITF	3801	hFzd5L
036S-D01-3	hFzd5L	RASQDISNWLA	2414	AASTLQS	3108	CQQANSFPLTF	3802	hFzd5L
036S-D02-5	hFzd5L	RASQGINNYLN	2415	AASSLQS	3109	CQQSYNTPFTF	3803	hFzd5L
036S-G03-3	hFzd5L	RASQGIAGWLA	2416	DASNLET	3110	CQQSYSTPLTF	3804	hFzd5L
040S-D07	hFzd6L	RASQSINRWLA	2417	AASTLQS	3111	CQQIHSYPLTF	3805	hFzd6L, mFzd6L
040S-E08	hFzd6L	RSSQSLLHSNGYNYLD	2418	AASSLQS	3112	CMQALQTPLTF	3806	hFzd6L, mFzd6L
040S-B09	hFzd6L	RASQTISNFLN	2419	AASSLQS	3113	CQQSYSPPYTF	3807	hFzd6L, mFzd6L
040S-H09	hFzd6L	RASQGISNYLN	2420	YASSLQS	3114	CQQTDSIPITF	3808	hFzd6L, mFzd6L
040S-E10	hFzd6L	RASQSISSYLN	2421	AASSLQS	3115	CQQSYNTPFTF	3809	hFzd6L, mFzd6L
040S-D11	hFzd6L	KSSQSVLYSSNNKNYLA	2422	STNTRSS	3116	CQQYYSIPVTF	3810	hFzd6L, mFzd6L
041S-B01	hFzd6L	RASQSIHSWLA	2423	AASNLQS	3117	CQQGYSTPPTF	3811	hFzd6L, mFzd6L
040S-E07	hFzd6L	RASQSISSYLN	2424	GASNLQR	3118	CQQSFSPPLTF	3812	hFzd6L, mFzd6L
040S-B08	hFzd6L	RASQSISSYLN	2425	AASSLQS	3119	CQQSYSTPLTF	3813	hFzd6L, mFzd6L
040S-F08	hFzd6L	KSSQSVLYSSNNKNYLA	2426	WASTRKS	3120	CHQYYSLPITF	3814	hFzd6L, mFzd6L

040S-B12	hFzd6L	RASQSVSNNYLA	2427	GASTRAT	3121	CHQYGSTPLTF	3815	hFzd6L, mFzd6L
040S-H06	hFzd6L	RASQSVSSNLA	2428	GASTRAT	3122	CQQYFSAPRTF	3816	hFzd6L, mFzd6L
040S-F07	hFzd6L	RASQGISNNLN	2429	GAYTLHS	3123	CQQSYTTLSTF	3817	hFzd6L, mFzd6L
040S-G08	hFzd6L	QASRDISNYLN	2430	GASSLQS	3124	CQQSYSAPLAF	3818	hFzd6L, mFzd6L
040S-B10	hFzd6L	RSSQSLLHSNGY NYLD	2431	AASTLQD	3125	CMQALQSPPTF	3819	hFzd6L, mFzd6L
040S-G10	hFzd6L	KSSQSVLYSSNN KNYLA	2432	WASDRES	3126	CQQYYSTPITF	3820	hFzd6L, mFzd6L
040S-C12	hFzd6L	RASQSISSWLA	2433	DASRLER	3127	CQKYNSAPLTF	3821	hFzd6L, mFzd6L
040S-A07	hFzd6L	RSSQSLLHSNGY NYLD	2434	AASSLQS	3128	CMQALQNPITF	3822	hFzd6L, mFzd6L
040S-G07	hFzd6L	RASQAISSYLA	2435	AASILQS	3129	CQQSSRTPPTF	3823	hFzd6L, mFzd6L
040S-C10	hFzd6L	RASQSISSYLN	2436	DASNLET	3130	CQQSHSAPITF	3824	hFzd6L, mFzd6L
040S-F12	hFzd6L	RASQSVSSYLA	2437	GASTRAT	3131	CQQYGNLITF	3825	hFzd6L, mFzd6L
040S-E11	hFzd6L	RASQSISSYLD	2438	AASSLQS	3132	CQQSYSSPLTF	3826	hFzd6L, mFzd6L
040S-G12	hFzd6L	RASQGISNYLA	2439	AASSLHS	3133	CQQYGNLPYTF	3827	hFzd6L, mFzd6L
041S-D01	hFzd6L	RASQSISSYLN	2440	AASSLQS	3134	CQQSYSTPITF	3828	hFzd6L, mFzd6L
040S-H07	hFzd6L	RSSRSLVYNANN KSYLA	2441	WASTRES	3135	CQQYYSVPLTF	3829	hFzd6L, mFzd6L
040S-C08	hFzd6L	RASESIGSYLN	2442	AASSLQS	3136	CQQANSFPPTF	3830	hFzd6L, mFzd6L
040S-H08	hFzd6L	RASQSISNWLA	2443	AASTLQS	3137	CQQSASPPPTF	3831	hFzd6L, mFzd6L
040S-C09	hFzd6L	QASQGISNYLA	2444	AASSLQS	3138	CQQSYSIPFTF	3832	hFzd6L, mFzd6L
040S-H10	hFzd6L	QASQSIYNYLN	2445	KASTLES	3139	CQQSYSIPFTF	3833	hFzd6L, mFzd6L
040S-F11	hFzd6L	QASQDISNYLN	2446	GASTLQS	3140	CEQSYSTPLTF	3834	hFzd6L, mFzd6L
041S-A01	hFzd6L	RSSQSVLSSSTYK NYLA	2447	WASTRES	3141	CQQYYATPFTF	3835	hFzd6L, mFzd6L
041S-E01	hFzd6L	RASRSIGPWLA	2448	ATSSLHG	3142	CQQSHSVPLTF	3836	hFzd6L, mFzd6L
040S-B07	hFzd6L	RSSQSLLHSNGY NYLD	2449	AASSLRS	3143	CMQSRHWPLTF	3837	hFzd6L, mFzd6L
040S-D08	hFzd6L	RASQSVSTWLA	2450	AASSLQS	3144	CQQSYSSPPTF	3838	hFzd6L, mFzd6L
040S-D09	hFzd6L	RVSQDISNSLN	2451	AASSLQS	3145	CQQSYSTPLTF	3839	hFzd6L, mFzd6L
040S-F09	hFzd6L	KSSQSVLYSSNN KNYLA	2452	WASTRES	3146	CQQYYDTPLTF	3840	hFzd6L, mFzd6L
040S-D10	hFzd6L	RASQGISNYLA	2453	KASSLES	3147	CQQTYAIPLTF	3841	hFzd6L, mFzd6L
040S-A11	hFzd6L	RASQSISSSYLA	2454	GASTRAT	3148	CQQYDNLPITF	3842	hFzd6L, mFzd6L
040S-D12	hFzd6L	RSSQSLLHSNGY NYLD	2455	LGSNRAS	3149	CMQALQTPYTF	3843	hFzd6L, mFzd6L
041S-F01	hFzd6L	RASQSISSYLN	2456	AASILEN	3150	CQQAHSFPLTF	3844	hFzd6L, mFzd6L
040S-B11	hFzd6L	RSSQSLLHSNGY NYLD	2457	AASSLQS	3151	CMQGTRWPPTF	3845	hFzd6L, mFzd6L
040S-G11	hFzd6L	QASQDISNYLN	2458	AASTLQS	3152	CQQSHSTPPTF	3846	hFzd6L, mFzd6L
040S-C07	hFzd6L	RASQSISTYLN	2459	AASSLQS	3153	CQQSYSTPWTF	3847	hFzd6L, mFzd6L
040S-A08	hFzd6L	RASQSINRWLA	2460	KASSLES	3154	CQQSYSIPFTF	3848	hFzd6L, mFzd6L

040S-A09	hFzd6L	QASQDISNYLN	2461	TASSLRS	3155	CQQANSFPITF	3849	hFzd6L, mFzd6L
040S-C11	hFzd6L	RASQSISSYLN	2462	ASSTLQS	3156	CQQSYSTPLTF	3850	hFzd6L, mFzd6L
040S-H11	hFzd6L	KSSQSVLYSSNN KNYLA	2463	WASTRES	3157	CQQYYSIPLTF	3851	hFzd6L, mFzd6L
041S-D02	hFzd6L	RSSQSLLHSNGY NYLD	2464	LGSNRAS	3158	CMQALQPPLTF	3852	hFzd6L, mFzd6L
041S-A04	hFzd6L	RASQGISNYLA	2465	GASTLQS	3159	CQQSFNGPLTF	3853	hFzd6L, mFzd6L
041S-A08	hFzd6L	QASQDISNYLN	2466	ATSSLQS	3160	CQQSYSIPPTF	3854	hFzd6L, mFzd6L
041S-F08	hFzd6L	RSSQSLLHSNGY NYLD	2467	AASSLQS	3161	CMQALQIPFTF	3855	hFzd6L, mFzd6L
041S-H01	hFzd6L	RASQNVNRWLA	2468	AASTLQS	3162	CQQSYSTPPTF	3856	hFzd6L, mFzd6L
041S-E02	hFzd6L	RASQSISSYLN	2469	DASTLQS	3163	CQQTSSTPLTF	3857	hFzd6L, mFzd6L
041S-C03	hFzd6L	RSSQSLLHSNGY NYLD	2470	LGSSRAS	3164	CMQGTQWPPTF	3858	hFzd6L, mFzd6L
041S-F06	hFzd6L	RASQGISNYLA	2471	AASSLQS	3165	CQQSYSTPLTF	3859	hFzd6L, mFzd6L
041S-F07	hFzd6L	RASQGISNYLA	2472	GTSNLET	3166	CQQYDRYPYIF	3860	hFzd6L, mFzd6L
041S-G08	hFzd6L	RASQGISSYLA	2473	AASNLQS	3167	CQQSYSTPLTF	3861	hFzd6L, mFzd6L
041S-F02	hFzd6L	RASQGINNYLA	2474	RASSLQR	3168	CQQSYTTPPTF	3862	hFzd6L, mFzd6L
041S-D03	hFzd6L	RASQTTKNYLN	2475	AASSLQS	3169	CQQSYRIPFSF	3863	hFzd6L, mFzd6L
041S-C05	hFzd6L	RAGQSIGSFLN	2476	DAKDLHP	3170	CQQSHTAPLTF	3864	hFzd6L, mFzd6L
041S-G06	hFzd6L	RASQAIRNDLA	2477	AASRLQS	3171	CQQSFATPRTF	3865	hFzd6L, mFzd6L
041S-C08	hFzd6L	RASQGISNYLA	2478	AASNLQS	3172	CQQYQSYPWTF	3866	hFzd6L, mFzd6L
041S-H08	hFzd6L	RASQSISSYLN	2479	DASNLET	3173	CQQSHSAPITF	3867	hFzd6L, mFzd6L
041S-E09	hFzd6L	RSSQSLLHSNGY NYLD	2480	AASSLQS	3174	CMQGTHWPPTF	3868	hFzd6L, mFzd6L
041S-G02	hFzd6L	RASQSVSSNYLA	2481	ATSARAT	3175	CQQYGTSPITF	3869	hFzd6L, mFzd6L
041S-C04	hFzd6L	RASQSVASSYLA	2482	GASTRAT	3176	CQQYGSSPITF	3870	hFzd6L, mFzd6L
041S-D05	hFzd6L	RASQSVSSYLA	2483	GASTRAT	3177	CQQYGSLPIAF	3871	hFzd6L, mFzd6L
041S-A06	hFzd6L	RASQSVSSSYLA	2484	GASTRAT	3178	CQQYGSSPITF	3872	hFzd6L, mFzd6L
041S-H06	hFzd6L	RASQSISSWLA	2485	AASNLQS	3179	CQQAKSFPPTF	3873	hFzd6L, mFzd6L
041S-F09	hFzd6L	RASQSISRYLN	2486	DATNLPT	3180	CQQANSFPLTF	3874	hFzd6L, mFzd6L
041S-B02	hFzd6L	RASQGISNYLA	2487	DASHLET	3181	CQQYDNLPLTF	3875	hFzd6L, mFzd6L
041S-H02	hFzd6L	RSSQSLLHSNGY NYLD	2488	LGSNRAS	3182	CMQGTHWPPTF	3876	hFzd6L, mFzd6L
041S-F03	hFzd6L	RSSQSLLHSNGY NYLD	2489	LGSNRAS	3183	CMQGTHWPLTF	3877	hFzd6L, mFzd6L
041S-D04	hFzd6L	RSSQSLLHSNGY NYLD	2490	AASSLQS	3184	CMQHTHWPPTF	3878	hFzd6L, mFzd6L
041S-G04	hFzd6L	RSSQSLLHSNGY NYLD	2491	KASSLEN	3185	CMQGSHWPPTF	3879	hFzd6L, mFzd6L
041S-E05	hFzd6L	RASQGISNYLA	2492	GASNLQS	3186	CQQSYSPPLTF	3880	hFzd6L, mFzd6L
041S-A07	hFzd6L	QASQDISNYLN	2493	AASTLQS	3187	CQQANSFPPSF	3881	hFzd6L, mFzd6L
041S-H07	hFzd6L	RSSQSLLHSNGY NYLD	2494	KASSLES	3188	CMQGLQTPVTF	3882	hFzd6L, mFzd6L

041S-D08	hFzd6L	RASQSISSYLN	2495	AASRLQS	3189	CQQSFRIPPTF	3883	hFzd6L, mFzd6L
041S-A09	hFzd6L	RASQGIRNDLG	2496	AASSLQS	3190	CQQSYSIPFTF	3884	hFzd6L, mFzd6L
041S-G03	hFzd6L	QASQDISDYLN	2497	AASTLQS	3191	CQQYYSTPITF	3885	hFzd6L, mFzd6L
041S-E04	hFzd6L	RSSQSLLHSNGY NYLD	2498	KASSLES	3192	CMQGTHWPLTF	3886	hFzd6L, mFzd6L
041S-H04	hFzd6L	RSSQSLLHSNGY NYLD	2499	LGSNRAS	3193	CMQVLQNPITF	3887	hFzd6L, mFzd6L
041S-F05	hFzd6L	QASQDISNYLA	2500	KASSLES	3194	CQQGYRTPPTF	3888	hFzd6L, mFzd6L
041S-C06	hFzd6L	RSSQSLLHSNGY NYLD	2501	LGSNRAS	3195	CMQALQTPPTF	3889	hFzd6L, mFzd6L
041S-B07	hFzd6L	RASQSVSSSYLA	2502	DISSRAS	3196	CQQYGSSPLTF	3890	hFzd6L, mFzd6L
041S-B09	hFzd6L	RASQSINTYLN	2503	AASTLHS	3197	CQQSFNTPLTF	3891	hFzd6L, mFzd6L
041S-H09	hFzd6L	RASQGIKNYLA	2504	AASTLKS	3198	CQQSYSPPRTF	3892	hFzd6L, mFzd6L
041S-A03	hFzd6L	KSSQSVLYRSNN KNYLA	2505	WASTRES	3199	CQQYYGLPYTF	3893	hFzd6L, mFzd6L
041S-A05	hFzd6L	RASQDISNYLN	2506	DASSLQS	3200	CQQSYSPPRTF	3894	hFzd6L, mFzd6L
041S-G05	hFzd6L	RSSRSLLHSNGY NYLD	2507	LGSDRAS	3201	CMQALQTPPTF	3895	hFzd6L, mFzd6L
041S-D06	hFzd6L	RASQSISSYLN	2508	AASTLQS	3202	CQQSYSIPYTF	3896	hFzd6L, mFzd6L
041S-C07	hFzd6L	QASQDISNYLN	2509	SASNLQS	3203	CQHSYSAPLTF	3897	hFzd6L, mFzd6L
041S-E08	hFzd6L	QASQDIRNHLN	2510	SVSNLQS	3204	CQQANTFPPAF	3898	hFzd6L, mFzd6L
041S-C09	hFzd6L	RASQSIANHLN	2511	AATTLRS	3205	CQQSYSAPYTF	3899	hFzd6L, mFzd6L
041S-A10	hFzd6L	RASQSIANHLN	2512	AATTLRS	3206	CQQSYSAPYTF	3900	hFzd6L, mFzd6L
041S-C02	hFzd6L	RASQGISSWLS	2513	AASNLQS	3207	CQQSFAPPRTF	3901	hFzd6L, mFzd6L
041S-B03	hFzd6L	RASQSIANHLN	2514	AATTLRS	3208	CQQSYSAPYTF	3902	hFzd6L, mFzd6L
041S-F04	hFzd6L	RASQSVGTYLA	2515	GASTRAT	3209	CQQYGSSALTF	3903	hFzd6L, mFzd6L
041S-B05	hFzd6L	RASQSISNWLA	2516	DASNLET	3210	CQQGSSFPLTF	3904	hFzd6L, mFzd6L
041S-E06	hFzd6L	RASQSISSYLN	2517	AASSLRS	3211	CQQSYSAPLTF	3905	hFzd6L, mFzd6L
041S-D07	hFzd6L	RASQSVSSYLA	2518	GASTRAT	3212	CQQYGSSPITF	3906	hFzd6L, mFzd6L
041S-B10	hFzd6L	RATQSVSSDYLA	2519	GASTRAT	3213	CQQYDNLPITF	3907	hFzd6L, mFzd6L
042S-F03	hFzd6L	TRSSGSIAZYYVQ	2520	EDDQRPS	3214	CQSYDRNSLVF	3908	hFzd6L, mFzd6L
041S-C10	hFzd6L	RSSQSLLHSNGY NYLD	2521	AASSLQS	3215	CMQSIQLPPTF	3909	hFzd6L, mFzd6L
041S-H10	hFzd6L	SGSKPNIGGHYV Y	2522	RNTQRPS	3216	CATWDDSLSGV VF	3910	hFzd6L, mFzd6L
042S-B02	hFzd6L	TRSSGSIASYYVQ	2523	EDDQRPS	3217	CQSYDRNSLVF	3911	hFzd6L, mFzd6L
042S-G03	hFzd6L	RSSKSLVYGDGN TYLN	2524	KVSNRDS	3218	CMQGTHWPPTF	3912	hFzd6L, mFzd6L
041S-D10	hFzd6L	TRSSGSIGDKYV Q	2525	QDDQRPS	3219	CQSYDSSNPHVV F	3913	hFzd6L, mFzd6L
041S-G11	hFzd6L	TGNSNNVGNRG AV	2526	RNNNRPS	3220	CSAWDSSLTVQV F	3914	hFzd6L, mFzd6L
042S-C01	hFzd6L	TRSSGSIGDKYV Q	2527	QDDQRPS	3221	CQSYDSSNPHVV F	3915	hFzd6L, mFzd6L
042S-A03	hFzd6L	SGDKLGDKFAY	2528	QDNKRPS	3222	CQAWDTGTAVF	3916	hFzd6L, mFzd6L

041S-B11	hFzd6L	RSSQSVZYSDVNCYLN	2529	KVSDLDY	3223	CMQGTHWPPTF	3917	hFzd6L, mFzd6L
042S-A04	hFzd6L	TGNSNNVGNRGAA	2530	RDNSRPS	3224	CSAWDSSLSVQVF	3918	hFzd6L, mFzd6L
041S-C11	hFzd6L	TGNSNNVGNRGAV	2531	RNNNRPS	3225	CSAWDSSLTVQVF	3919	hFzd6L, mFzd6L
042S-D03	hFzd6L	TRSSGSIGDKYVQ	2532	QDDQRPS	3226	CQSYDSSNPHVVF	3920	hFzd6L, mFzd6L
042S-F04	hFzd6L	TRNSGNIATAYVQ	2533	QDFQRPS	3227	CQSYDNNYRAVF	3921	hFzd6L, mFzd6L
042S-D01	hFzd6L	SGSSSNIGSNAVN	2534	GSNERPS	3228	CAAWDDRFNGFALF	3922	hFzd6L, mFzd6L
042S-H01	hFzd6L	TRSSGSIGDKYVQ	2535	QDDQRPS	3229	CQSYDSSNPHVVF	3923	hFzd6L, mFzd6L
042S-C05	hFzd6L	TRSSGSIGDKYVQ	2536	QDDQRPS	3230	CQSYDSSNPHVVF	3924	hFzd6L, mFzd6L
041S-E11	hFzd6L	TGNSNNVGNRGAV	2537	RNNNRPS	3231	CSAWDSSLTVQVF	3925	hFzd6L, mFzd6L
041S-B12	hFzd6L	TRSSGSIGDKYVQ	2538	QDDQRPS	3232	CQSYDSSNPHVVF	3926	hFzd6L, mFzd6L
041S-G12	hFzd6L	TGNNYNVGNAGAA	2539	RNNDRPS	3233	CSAWDSSLKVQVF	3927	hFzd6L, mFzd6L
042S-E01	hFzd6L	TRNSGNIATAYVQ	2540	QDFQRPS	3234	CQSYDNNYRAVF	3928	hFzd6L, mFzd6L
042S-B04	hFzd6L	RSSQSLLHSNGYNYLD	2541	LGSNRAS	3235	CMQALQTPRSF	3929	hFzd6L, mFzd6L
041S-G10	hFzd6L	TGNSNNVGNAGAV	2542	RSNNRPS	3236	CSAWDTSLRVQVF	3930	hFzd6L, mFzd6L
042S-A02	hFzd6L	TRSSGSIGDKYVQ	2543	QDDQRPS	3237	CQSYDSSNPHVVF	3931	hFzd6L, mFzd6L
042S-C03	hFzd6L	TGNSNNVGNRGAV	2544	RNNNRPS	3238	CSAWDSSLTVQVF	3932	hFzd6L, mFzd6L
042S-C04	hFzd6L	RSSKSLVYZDGNTYLN	2545	KVSNRDS	3239	CMQGTHWPPTF	3933	hFzd6L, mFzd6L
042S-H07	hFzd6L	TGTISDVGGYNYVS	2546	EVSHRPS	3240	CNSYTSSSTVIF	3934	hFzd6L, mFzd6L
042S-G08	hFzd6L	SGNSNNVGYAGAA	2547	RNNDRPS	3241	CSAWDSSLKVQVF	3935	hFzd6L, mFzd6L
042S-H09	hFzd6L	SGNSNNVGYGGAV	2548	RNNNRPS	3242	CSAWDSSLSAQVF	3936	hFzd6L, mFzd6L
042S-D10	hFzd6L	RSSQSLLHSNGYNYLD	2549	LGSNRAS	3243	CMQALRTPYTF	3937	hFzd6L, mFzd6L
042S-G10	hFzd6L	SGNSNNVGYGGAV	2550	RNNNRPS	3244	CSAWDSSLSAQVF	3938	hFzd6L, mFzd6L
042S-A08	hFzd6L	RSSQSLLHSNGYNYLD	2551	LGSNRAS	3245	CMQSIQLPLTF	3939	hFzd6L, mFzd6L
042S-H08	hFzd6L	TGNNYNVGNAGAA	2552	RNNDRPS	3246	CSSWDNSLSAQVF	3940	hFzd6L, mFzd6L
042S-E09	hFzd6L	TGNNYNVGNAGAA	2553	RNNDRPS	3247	CSAWDSSLKVQVF	3941	hFzd6L, mFzd6L
042S-A06	hFzd6L	TGNSNNVGNRGAV	2554	RNNNRPS	3248	CSAWDSSLTVQVF	3942	hFzd6L, mFzd6L
042S-F06	hFzd6L	SGKNYZVGNAGAA	2555	RNNDRPS	3249	CSAWDSSLKVQVF	3943	hFzd6L, mFzd6L
042S-B08	hFzd6L	RSSKSLVYSDGNTYLN	2556	KVSNRDS	3250	CMQGTHWPPTF	3944	hFzd6L, mFzd6L
042S-A09	hFzd6L	TGNNYNVGNAGAA	2557	RNNDRPS	3251	CSSWDNSLSAQVF	3945	hFzd6L, mFzd6L
042S-H10	hFzd6L	SGNNNNVGFAGAA	2558	RNNDRPS	3252	CSAWDSSLKVQVF	3946	hFzd6L, mFzd6L
042S-D07	hFzd6L	KSSKSLVYGDGNTYLN	2559	KVSNRDS	3253	CMQGTHWPPTF	3947	hFzd6L, mFzd6L
042S-B09	hFzd6L	SGNSNNVGYGGAV	2560	RNNNRPS	3254	CSAWDSSLSAQVF	3948	hFzd6L, mFzd6L
042S-A11	hFzd6L	SGSSSNIGNNHVS	2561	ANNKRPS	3255	CGTWDGSLSSGVF	3949	hFzd6L, mFzd6L
042S-H06	hFzd6L	TGNSNNVGNRGAV	2562	RNNNRPS	3256	CSAWDSSLTVQVF	3950	hFzd6L, mFzd6L

042S-E07	hFzd6L	TGNSNNVGNRGAV	2563	RNNNRPS	3257	CSAWDSSLTVQVF	3951	hFzd6L, mFzd6L
042S-D08	hFzd6L	TGSSNNVGNAGAA	2564	RNNDRPS	3258	CSSWDSSLKVQLF	3952	hFzd6L, mFzd6L
042S-F09	hFzd6L	TRSGGGIASSFVQ	2565	QDDQRPS	3259	CQSYGSGFVVF	3953	hFzd6L, mFzd6L
042S-A10	hFzd6L	SGSTSNIGYSFVS	2566	DNSKRPS	3260	CAAWDLPLNAVVF	3954	hFzd6L, mFzd6L
042S-C09	hFzd6L	TGNNYNVGNAGAA	2567	RNNDRPS	3261	CSAWDSSLKVQVF	3955	hFzd6L, mFzd6L
042S-F10	hFzd6L	SGSSSNIGNNYVS	2568	ENNKRPS	3262	CGTWDSSLSAVVF	3956	hFzd6L, mFzd6L
042S-D11	hFzd6L	TGNNYNVGNAGAA	2569	RNNDRPS	3263	CSAWDSSLKVQVF	3957	hFzd6L, mFzd6L
042S-F07	hFzd6L	TGTSSDVGGYNYVS	2570	GVSNRPS	3264	CSSYTRSSTLLF	3958	hFzd6L, mFzd6L
042S-E08	hFzd6L	RSSQSLLHSNGYNYLD	2571	LGSNRAS	3265	CMQALQTSYTF	3959	hFzd6L, mFzd6L
042S-B10	hFzd6L	TGNSNNVGKGGAA	2572	RTLDRPS	3266	CSAWDSSLRVQVF	3960	hFzd6L, mFzd6L
042S-B11	hFzd6L	TGNNYNVGNAGAA	2573	RNNDRPS	3267	CSSWDNSLSAQVF	3961	hFzd6L, mFzd6L
042S-F11	hFzd6L	TRSSGSIASNYVQ	2574	DDNQRPS	3268	CQSYDSSSVVF	3962	hFzd6L, mFzd6L
042S-B07	hFzd6L	TGNSNNVGNRGAV	2575	RNNNRPS	3269	CSAWDSSLTVHVF	3963	hFzd6L, mFzd6L
042S-G07	hFzd6L	KSSQSLLYFNGNTYLS	2576	QVSNRDS	3270	CMQGTQWPPTF	3964	hFzd6L, mFzd6L
042S-F08	hFzd6L	TRSSGSIASNYVR	2577	DDDQRPS	3271	CQSFDTSNQVF	3965	hFzd6L, mFzd6L
042S-C10	hFzd6L	TGNNYNVGNAGAA	2578	RNNDRPS	3272	CSSWDNSLSAQVF	3966	hFzd6L, mFzd6L
043S-D05	hFzd6L	RSSQSLVYSDGDTYLN	2579	KVSKRDS	3273	CMQGTHWPPTF	3967	hFzd6L, mFzd6L
043S-H04	hFzd6L	TGSSSNIGAGYDVH	2580	GNSNRPS	3274	CQSYDSSLSGWVF	3968	hFzd6L, mFzd6L
043S-G08	hFzd6L	TGSSSNIGAGYDVH	2581	GNSNRPS	3275	CQSYDSSLSGWVF	3969	hFzd6L, mFzd6L
043S-D09	hFzd6L	RSSQSLVHSDGNTYLN	2582	QVSNRDS	3276	CMQGTHWPPTF	3970	hFzd6L, mFzd6L
043S-E09	hFzd6L	TRSSGSIGDKYVQ	2583	QDDQRPS	3277	CQSYDSSNPHVVF	3971	hFzd6L, mFzd6L
043S-F07	hFzd6L	TGNSNNVGNRGAV	2584	RNNNRPS	3278	CSAWDSSLTVQVF	3972	hFzd6L, mFzd6L
043S-H07	hFzd6L	TGNSNNVGNRGAV	2585	RNNNRPS	3279	CSAWDSSLTVQVF	3973	hFzd6L, mFzd6L
043S-F08	hFzd6L	TGNNYNVGNAGAA	2586	RNNDRPS	3280	CSAWDSSLKVQVF	3974	hFzd6L, mFzd6L
043S-C09	hFzd6L	TGNSNNVGKGGAA	2587	RTLDRPS	3281	CSAWDSSLRVQVF	3975	hFzd6L, mFzd6L
031S-G02	hFzd7ext	RSSQSLVYSDGNTYLN	2588	KVSNRDS	3282	CMQGTHWPPTF	3976	hFzd7L
031S-A03	hFzd7ext	RSSQSLLHSNGYNYLD	2589	SASNLQS	3283	CMQSLQTPVTF	3977	hFzd7L
031S-B03	hFzd7ext	RSSQSLLHSNGYNYLD	2590	LGSKRPS	3284	CMQALQTPITF	3978	hFzd7L
031S-C03	hFzd7ext	RASQGIRNDLA	2591	AASSLQS	3285	CQQIHSYPLTF	3979	hFzd7L
031S-D03	hFzd7ext	RSSQSLLHSNGYNYLD	2592	EVSNRAS	3286	CMQGSHWPPTF	3980	hFzd7L
031S-E03	hFzd7ext	RSSQSLLHSNGYNYLD	2593	AASSLQS	3287	CMQALQTPITF	3981	hFzd7L
031S-F03	hFzd7ext	RSSQSLLHSNGYNYLD	2594	AASSLQS	3288	CMQSIQLPITF	3982	hFzd7L
031S-G03	hFzd7ext	RSSQSLLHSNGYNYLD	2595	AASSLQS	3289	CMQALQTPITF	3983	hFzd7L
031S-H03	hFzd7ext	RASQSISSYLN	2596	AASTLQS	3290	CQQANSFPLTF	3984	hFzd2L,7L
031S-A04	hFzd7ext	RSSQSLLHSNGYNYLD	2597	DASNLET	3291	CMQALQTPLTF	3985	hFzd7L

031S-C04	hFzd7ext	RSSQSLLHSNGYNYLD	2598	AASSLQS	3292	CMQSLQTPITF	3986	hFzd7L
031S-D04	hFzd7ext	RSSQSLLHSNGYNYLD	2599	DASSLES	3293	CMQALQTPLTF	3987	hFzd7L
031S-E04	hFzd7ext	RASQNIGTWLA	2600	AASSLQS	3294	CQQSYSSPLTF	3988	hFzd7L
031S-F04	hFzd7ext	RSSQSLLHSNGYNYLD	2601	LGSNRAS	3295	CMQAVQVPITF	3989	hFzd2L,7L
031S-G04	hFzd7ext	RSSQSLLHSNGYNYLD	2602	AASSLQS	3296	CMQALQTPLTF	3990	hFzd7L
031S-H04	hFzd7ext	QASQEISNYLN	2603	AASKLHS	3297	CQQSYSSPLTF	3991	hFzd7L
031S-A05	hFzd7ext	RSSQSLLHSNGYNYLD	2604	AASTLHT	3298	CMQTLQTPFTF	3992	hFzd7L
031S-B05	hFzd7ext	KSSQSVLYGSNNKNYLA	2605	WASTRKS	3299	CQQYYSFPLTF	3993	hFzd7L
031S-C05	hFzd7ext	RSSQSLLHSNGYNYLD	2606	DASNLET	3300	CMQALQTPLTF	3994	hFzd7L
031S-D05	hFzd7ext	KSSQSVLYSSNNKNYLA	2607	WASTRES	3301	CQQYFTPPITF	3995	hFzd7L
031S-E05	hFzd7ext	RSSQSLLHSNGYNYLD	2608	LGSNRAS	3302	CMQSTQLPWTF	3996	hFzd7L
031S-F05	hFzd7ext	RASQSINTHLN	2609	AASSLQS	3303	CQQSYSTPLTF	3997	hFzd2L,7L
031S-G05	hFzd7ext	RASQSISTWLA	2610	AASSLQS	3304	CQQSYSPPITF	3998	hFzd7L
031S-A06	hFzd7ext	RSSQSLLHSNGYNYLD	2611	AASTLQP	3305	CMQALQTPITF	3999	hFzd7L
031S-B06	hFzd7ext	RSSQSLLHSNGYNYLD	2612	LGSLRAS	3306	CMQALQTPTF	4000	hFzd7L
031S-D06	hFzd7ext	RASQSVSSWLA	2613	AASSLQS	3307	CQQSYSAPLTF	4001	hFzd7L
031S-E06	hFzd7ext	RSSQSLLHSNGYNYLD	2614	LGSTRAS	3308	CMQALQTPTF	4002	hFzd7L
031S-F06	hFzd7ext	RASQGISSYLA	2615	AASNLHN	3309	CQQSYSTPLTF	4003	hFzd7L
031S-G06	hFzd7ext	RSSQSLLHSNGYNYLD	2616	AASSLQS	3310	CMQALQTPITF	4004	hFzd1L,2L,7L
031S-A07	hFzd7ext	RSSQSLLHSNGYNYLD	2617	AASSLQS	3311	CMQALQIPLTF	4005	hFzd7L
031S-C07	hFzd7ext	QASQDISNYLN	2618	AASTLQS	3312	CQQSYTIPITF	4006	hFzd1L,2L,7L
031S-E07	hFzd7ext	RASQGVSSYLA	2619	GASARAT	3313	CQQYGSSPITF	4007	hFzd1L,2L,7L
031S-H07	hFzd7ext	RSSQSLLHSNGYNYLD	2620	AASSLES	3314	CMQALQTPLTF	4008	hFzd7L
031S-A08	hFzd7ext	RASQSISSWLA	2621	AASSLQS	3315	CQQSHSAPITF	4009	hFzd2L,7L
031S-B08	hFzd7ext	QASQDIGNYLN	2622	GASTLQS	3316	CQQSYSTPLTF	4010	hFzd7L
031S-C08	hFzd7ext	RASQGISNYLN	2623	GASSLQR	3317	CQQSYSMPLTF	4011	hFzd2L,7L
031S-D08	hFzd7ext	RVSQGISNYLA	2624	DASNLET	3318	CQQSYSPPFTF	4012	hFzd7L
031S-E08	hFzd7ext	RSSQSLLHSNGYNYLD	2625	LGSNRAS	3319	CMQGRQTPTF	4013	hFzd7L
031S-F08	hFzd7ext	RASQSISRWLA	2626	AASSLQS	3320	CQQAYTFPLTF	4014	hFzd7L
031S-G08	hFzd7ext	RSSQSLLHSNGYNYLD	2627	AASSLQS	3321	CMQALQIPITF	4015	hFzd7L
031S-H08	hFzd7ext	XASQDISNYLN	2628	DASSLES	3322	CQQANSFPLTF	4016	hFzd1L,2L,7L
032S-G01	mFzd7L	RSSQSLLHSNGYNYLD	2629	LASNRAS	3323	CMQALQTPTF	4017	hFzd7L, mFzd7L
032S-H01	mFzd7L	RASQSINNWLA	2630	SASSLQS	3324	CQQSYDTPITF	4018	hFzd7L, mFzd7L
032S-A02	mFzd7L	RSSQSLLHSNGYNYLD	2631	GWMNPYSGNTGYA	3325	CMQALQTPYTF	4019	hFzd7L, mFzd7L
032S-B02	mFzd7L	RSSQSLLHSNGYNYLD	2632	LGSNRAS	3326	CMQALQTPTF	4020	hFzd7L, mFzd7L
032S-F02	hFzd7L	RSSQSLLHSNGYNYLD	2633	AASNLET	3327	CMQARQAPYTF	4021	hFzd7L
032S-D02	hFzd7L	RSSQSLLHSNGYNYLD	2634	LGSNRAS	3328	CMQALQTPTF	4022	hFzd7L, mFzd7L

032S-H02	hFzd7L	RASQNISSYLN	2635	DASTLQS	3329	CQQSYSPPFTF	4023	hFzd7L, mFzd7L
032S-A03	hFzd7L	RASQGISSHLA	2636	KASSLES	3330	CLQHYSYPLTF	4024	hFzd7L
049S-B02	hFzd7L	RSSQSLLHSNGY NYLD	2637	LGSNRAS	3331	CMQALQAPTF	4025	hFzd7L, mFzd7L
049S-D02	hFzd7L	RASQAISNYLV	2638	DASTLQS	3332	CQQSYSTPFTF	4026	hFzd7L, mFzd7L
049S-F02	hFzd7L	KSSQSVLYSSNN KNYLA	2639	WASTRES	3333	CQQYYTTPITF	4027	hFzd7L, mFzd7L
049S-H02	hFzd7L	RSSQSLLHSNGY NYLD	2640	LGSNRAS	3334	CMQALQTPTF	4028	hFzd7L, mFzd7L
049S-A03	hFzd7L	RSSQSLLHSNGY NYLD	2641	LGSNRAS	3335	CMQALQTPLTF	4029	hFzd7L, mFzd7L
049S-B03	hFzd7L	KSSQSVLYSSNN KNYLA	2642	WASARES	3336	CQQYYSVPVTF	4030	hFzd7L, mFzd7L
049S-C03	hFzd7L	RASQSISSYLN	2643	AASSLQS	3337	CQQSYSTPLTF	4031	hFzd7
049S-E03	hFzd7L	RSSQSLLHSNGY NYLD	2644	LGSNRAS	3338	CMQALQTPITF	4032	hFzd7L, mFzd7L
049S-F03	hFzd7L	RSSQSLLHSNGY NYLD	2645	LGSNRAS	3339	CMQALQTPHTF	4033	hFzd7L, mFzd7L
049S-H03	hFzd7L	RSSQSLLHSNGY NYLD	2646	LGSDRAS	3340	CMQALQTPITF	4034	hFzd7L, mFzd7L
049S-A04	hFzd7L	RSSQSLLHSNGY NYLD	2647	LGSNRAS	3341	CMQALQTPLTF	4035	hFzd7L, mFzd7L
049S-B04	hFzd7L	RSSQSLLHSNGY NYLD	2648	DASNLVT	3342	CMQALQIPPTF	4036	hFzd7L, mFzd7L
049S-C04	hFzd7L	RSSQSLLHSNGY NYLD	2649	LASNRAS	3343	CMQALQTPTF	4037	hFzd7L, mFzd7L
15G4-4	mFzd8L	KSSQSLLDSDGKT YLN	2650	LVSKLDS	3344	CWQGTHFPYTF	4038	mFzd8L
027S-E5	hFzd8	RASQGITKSLA	2651	AASNLAT	3345	CQQYNTFPITF	4039	hFzd8
037S-A01	hFzd9L	RSSRSLLHSDGN TYLH	2652	LGSNRAS	3346	CAQVLQLPYTF	4040	hFzd9L
050S-A01	hFzd9L	QASQDISNYLN	2653	GASRLET	3347	CQQSYSTPLTF	4041	hFzd9, mFzd9
050S-B01	hFzd9L	RSSQSLRVSNGA ZYLD	2654	LGSNZQS	3348	CMQSFQPPFTF	4042	hFzd9, mFzd9
050S-C01	hFzd9L	RASQZISRWLA	2655	DASTLQS	3349	CQQSYSTPLTF	4043	hFzd9, mFzd9
050S-D01	hFzd9L	QASQDISZYLT	2656	RVSSLQT	3350	CQQSYNTPFTF	4044	hFzd9, mFzd9
050S-E01	hFzd9L	RSSQSLLHSNGY NYLD	2657	DATNLPT	3351	CMQALQIPYTF	4045	hFzd9, mFzd9
050S-F01	hFzd9L	RASQGISNNLN	2658	AASSLQS	3352	CQQANSFPHTF	4046	hFzd9, mFzd9
050S-G01	hFzd9L	RASQGISNYLA	2659	GASSRQS	3353	CQQDYSNPLTF	4047	hFzd9, mFzd9
050S-H01	hFzd9L	RSSQSLLHSNGY NYLD	2660	DASSLQS	3354	CMQALQAPLTF	4048	hFzd9, mFzd9
050S-A02	hFzd9L	RASQSISRWLA	2661	DASTLQS	3355	CQQSYSTPLTF	4049	hFzd9, mFzd9
050S-B02	hFzd9L	RASQSISSWLA	2662	GASTLQS	3356	CQQCYDTPLTF	4050	hFzd9, mFzd9
050S-C02	hFzd9L	RSSQSVLYSSNN KNYLA	2663	WASTRES	3357	CQQYYSTPPTF	4051	hFzd9, mFzd9
050S-D02	hFzd9L	KSSQSVLYSSNN KNYLA	2664	WASTRES	3358	CQQYFSIPLTF	4052	hFzd9, mFzd9
050S-E02	hFzd9L	RASQNINNWLA	2665	GASSLET	3359	CQQAYSFPFTF	4053	hFzd9, mFzd9
050S-F02	hFzd9L	QZSQDISNYLN	2666	ZASRWQS	3360	CQQAYSFPLTF	4054	hFzd9, mFzd9
050S-G02	hFzd9L	RASQSINRWLA	2667	GASTLES	3361	CQQSYSTPLTF	4055	hFzd9, mFzd9
050S-H02	hFzd9L	RSSQSLLHSNGY NYLD	2668	LGSNRAS	3362	CMQSLQPPFTF	4056	hFzd9, mFzd9
050S-A03	hFzd9L	RASQSINRWLA	2669	DASTLQS	3363	CQQSYSTPLTF	4057	hFzd9, mFzd9

050S-B03	hFzd9L	KSZQZVLYZSNNKNYLZ	2670	ZASTRES	3364	CQQYYSTPLTF	4058	hFzd9, mFzd9
050S-C03	hFzd9L	RASQSISSYLN	2671	AASILQT	3365	CQQDYNSPLTF	4059	hFzd9, mFzd9
050S-D03	hFzd9L	RASQSISRWLA	2672	DASTLQS	3366	CQQSYSTPLTF	4060	hFzd9, mFzd9
050S-E03	hFzd9L	RASQSINZZLA	2673	GASTLQS	3367	CQQDYSTPFTF	4061	hFzd9, mFzd9
050S-F03	hFzd9L	RASQSISSWLA	2674	AASSLQS	3368	CQQSYSTPFTF	4062	hFzd9, mFzd9
050S-G03	hFzd9L	RASQSISRWLA	2675	DASTLQS	3369	CQQSYSTPLTF	4063	hFzd9, mFzd9
050S-H03	hFzd9L	RASQSINRWLA	2676	SASTLES	3370	CQQDYSTPLTF	4064	hFzd9, mFzd9
050S-A04	hFzd9L	RASZGISNZLN	2677	AASSLQS	3371	CQQANSFPHTF	4065	hFzd9, mFzd9
050S-B04	hFzd9L	KSSQSVLYSSNNKNYLA	2678	WASARHS	3372	CHQYYSVPFTF	4066	hFzd9, mFzd9
050S-C04	hFzd9L	RASQSISTWLA	2679	GASTLHS	3373	CQQSYDTPFTF	4067	hFzd9, mFzd9
050S-D04	hFzd9L	RASQSISRWLA	2680	DASTLQS	3374	CQQSYSTPLTF	4068	hFzd9, mFzd9
050S-E04	hFzd9L	RASQGISNNLN	2681	AASSLQS	3375	CQQANSFPPTF	4069	hFzd9, mFzd9
050S-F04	hFzd9L	QASQDISNYLN	2682	DGSFLET	3376	CQQANSFPLTF	4070	hFzd9, mFzd9
050S-G04	hFzd9L	KSSQSVLYSSNNKNYLA	2683	WASTRES	3377	CQQYYRTPITF	4071	hFzd9, mFzd9
050S-H04	hFzd9L	RASQSINZYLA	2684	SASZLES	3378	CQQAYSFPLTF	4072	hFzd9, mFzd9
050S-A05	hFzd9L	RASQSIASYLN	2685	DASNLET	3379	CQQSYSTPFTF	4073	hFzd9, mFzd9
050S-B05	hFzd9L	RASZZISSYLZ	2686	AASTLQS	3380	CQQDYSYPLTF	4074	hFzd9, mFzd9
050S-C05	hFzd9L	RASQGISSYLA	2687	GASSLQS	3381	CQQSYSTPFTF	4075	hFzd9, mFzd9
050S-D05	hFzd9L	RSSQSLLHSNGYNYLD	2688	DASNLET	3382	CMQATQFPYTF	4076	hFzd9, mFzd9
050S-E05	hFzd9L	RASQSVGHFLA	2689	AASRLQT	3383	CLQDYDYPLTF	4077	hFzd9, mFzd9
050S-F05	hFzd9L	ZASQDIZNYLN	2690	GASSLQS	3384	CQQANSFPFTF	4078	hFzd9, mFzd9
050S-G05	hFzd9L	RVSQGISSYLN	2691	AASSLQS	3385	CQQGYSTPFTF	4079	hFzd9, mFzd9
050S-H05	hFzd9L	QASQDISNYLN	2692	DASNLET	3386	CQQAYDFPLTF	4080	hFzd9, mFzd9
050S-A06	hFzd9L	RASQGISNYLA	2693	GASNLQS	3387	CQQSYDTPLTF	4081	hFzd9, mFzd9
050S-B06	hFzd9L	QASQDISNYLN	2694	GASSLQS	3388	CQQANSFPFTF	4082	hFzd9, mFzd9
050S-C06	hFzd9L	QASQDISNYLN	2695	RVSSLQT	3389	CQQSYNTPFTF	4083	hFzd9, mFzd9
050S-D06	hFzd9L	KSSQTVLYNSNNKNYLA	2696	WASTRES	3390	CQQYYSTPLTF	4084	hFzd9, mFzd9
050S-E06	hFzd9L	RASQSISTWLA	2697	KASSLES	3391	CQQSYSTPFTF	4085	hFzd9, mFzd9
050S-F06	hFzd9L	KSSQSVLYNSNNKNYLA	2698	WASTRDS	3392	CQQYYSPPLTF	4086	hFzd9, mFzd9
050S-G06	hFzd9L	RASQGISNNLN	2699	AASSLQS	3393	CQQANSFPPTF	4087	hFzd9, mFzd9
050S-A07	hFzd9L	RASQGISNYLA	2700	AASSLQS	3394	CQQGNNFPWTF	4088	hFzd9, mFzd9
050S-B07	hFzd9L	RASENINSWLA	2701	AASRLQS	3395	CQQSYSSWWTF	4089	hFzd9, mFzd9
050S-D07	hFzd9L	RASQGISSWLA	2702	DASNLET	3396	CQQSYDSPLTF	4090	hFzd9, mFzd9
050S-E07	hFzd9L	LSSSNNNNYLA	2703	WASTRQS	3397	CQQDYSFPITF	4091	hFzd9, mFzd9

050S-F07	hFzd9L	RASQZISNNLN	2704	AASSLQS	3398	CQQANSFPPTF	4092	hFzd9, mFzd9
050S-G07	hFzd9L	RSSQSLLHSNGYNYLD	2705	LGSNRAS	3399	CMQALQTPITF	4093	hFzd9, mFzd9
050S-A08	hFzd9L	KSSQSVLYSSNNKNYLA	2706	WASTRES	3400	CQQYYRTPITF	4094	hFzd9, mFzd9
050S-B08	hFzd9L	RASQFISSWLA	2707	GASSLQS	3401	CQQSYNTPFTF	4095	hFzd9, mFzd9
050S-C08	hFzd9L	QASQDISNYLN	2708	AASSLQS	3402	CQQSYNTPFTF	4096	hFzd9, mFzd9
050S-D08	hFzd9L	RASQSISRWLA	2709	DASTLQS	3403	CQQSYSTPLTF	4097	hFzd9, mFzd9
050S-E08	hFzd9L	RASQSISRWLA	2710	DASNLET	3404	CQQSYNTPITF	4098	hFzd9, mFzd9
050S-F08	hFzd9L	KSSQSVLYSSNNKNYLA	2711	WASTRES	3405	CQQYYSTPLTF	4099	hFzd9, mFzd9
050S-G08	hFzd9L	RASESIGSWLA	2712	SASTLQS	3406	CQQSYNTPWTF	4100	hFzd9, mFzd9
050S-H08	hFzd9L	RASQGISNNLN	2713	AASSLQS	3407	CQQANSFPPTF	4101	hFzd9, mFzd9
050S-A09	hFzd9L	RASQSISZWLA	2714	DASTLQS	3408	CQQSYSTPLTF	4102	hFzd9, mFzd9
050S-B09	hFzd9L	RASQGISNNLN	2715	AASSLQS	3409	CQQANSFPPTF	4103	hFzd9, mFzd9
050S-C09	hFzd9L	RASQEISSWLA	2716	GASSLQS	3410	CQQANSFPWTF	4104	hFzd9, mFzd9
050S-D09	hFzd9L	RASZZISNNLN	2717	AASSLQS	3411	CQQANSFPPLF	4105	hFzd9, mFzd9
050S-E09	hFzd9L	RASQSISSWLA	2718	EVSNRFS	3412	CQQSYSIPITF	4106	hFzd9, mFzd9
050S-F09	hFzd9L	QASQDISNYLN	2719	AASRLQS	3413	CQQAYSFPLTF	4107	hFzd9, mFzd9
050S-G09	hFzd9L	RASZGISNNLN	2720	AASSLQS	3414	CQQANSFPPTF	4108	hFzd9, mFzd9
050S-H09	hFzd9L	RASQDITNYLN	2721	SASSLHS	3415	CQQTDSIPITF	4109	hFzd9, mFzd9
050S-A10	hFzd9L	KSSQSVLYSSNNKNYLA	2722	WASTRES	3416	CQQYYSTPPTF	4110	hFzd9, mFzd9
050S-B10	hFzd9L	RASQSINRWLA	2723	DASTLQS	3417	CQQSYSTPLTF	4111	hFzd9, mFzd9
050S-C10	hFzd9L	RASQGISNNLN	2724	AASSLQS	3418	CQQANSFPPTF	4112	hFzd9, mFzd9
050S-D10	hFzd9L	RASQGISNYLA	2725	AASSLQS	3419	CQQANNFPWTF	4113	hFzd9, mFzd9
050S-E10	hFzd9L	RASQSINRWLA	2726	DASTLQS	3420	CQQSYSTPLTF	4114	hFzd9, mFzd9
050S-F10	hFzd9L	RASQSISSYLN	2727	QASSLES	3421	CLQDYNYPFTF	4115	hFzd9, mFzd9
050S-G10	hFzd9L	RSSQSLZHSNGYNYLD	2728	LASNRAS	3422	CMQGLQPPFTF	4116	hFzd9, mFzd9
050S-H10	hFzd9L	KSSQSVLYSSNNKNYLA	2729	WASTRAS	3423	CQQYYSTPLTF	4117	hFzd9, mFzd9
050S-A11	hFzd9L	RASQSIGYWLA	2730	SASNLQS	3424	CQQAYSFPWTF	4118	hFzd9, mFzd9
050S-B11	hFzd9L	RASQGISNNLN	2731	KASSLES	3425	CQQANSFPPTF	4119	hFzd9, mFzd9
050S-C11	hFzd9L	RASQSITRWLA	2732	DASTLQS	3426	CQQSYSTPLTF	4120	hFzd9, mFzd9
050S-D11	hFzd9L	RASQSISRWLA	2733	DASTLQS	3427	CQQSYSTPLTF	4121	hFzd9, mFzd9
050S-E11	hFzd9L	RASZZISNZLN	2734	AASSLZS	3428	CQQANSFPPTF	4122	hFzd9, mFzd9
050S-F11	hFzd9L	RASQGIDNWLA	2735	AASSLQS	3429	CQQSYNLPLTF	4123	hFzd9, mFzd9
050S-G11	hFzd9L	RASQSISSYLN	2736	AASILHS	3430	CLQDYSYPLTF	4124	hFzd9, mFzd9
050S-H11	hFzd9L	RASQSISTYLN	2737	AASSLQS	3431	CQQSYSFPFTF	4125	hFzd9, mFzd9

050S-A12	hFzd9L	RASQSISRWLA	2738	DASTLQS	3432	CQQSYSTPLTF	4126	hFzd9, mFzd9
050S-B12	hFzd9L	RASQNIATYLN	2739	QASSLES	3433	CQQSYDTPFTF	4127	hFzd9, mFzd9
050S-C12	hFzd9L	RASQEISSWLA	2740	GASSLQS	3434	CQQANSFPWTF	4128	hFzd9, mFzd9
050S-D12	hFzd9L	RSSQSLLHSNGY NYLD	2741	LASNRAS	3435	CMQGLQPPFTF	4129	hFzd9, mFzd9
050S-E12	hFzd9L	RASQSIYRWLZ	2742	SASTLES	3436	CQQAYSTPLTF	4130	hFzd9, mFzd9
050S-F12	hFzd9L	RAZQGISNNLN	2743	AASSLQS	3437	CQQANSFPPTF	4131	hFzd9, mFzd9
050S-G12	hFzd9L	RASQSIYRWLA	2744	SASTLES	3438	CQQAYSTPLTF	4132	hFzd9, mFzd9
051S-A01	hFzd9L	RASQGISIYLA	2745	SASNLQS	3439	CQQAYSFPFTF	4133	hFzd9, mFzd9
051S-B01	hFzd9L	KSSQSVLYSSNN KNYLA	2746	WASTRES	3440	CQQYYSTPLTF	4134	hFzd9, mFzd9
051S-C01	hFzd9L	RASQSISSWLA	2747	AASNLEI	3441	CQQSYSTPFTF	4135	hFzd9, mFzd9
051S-E01	hFzd9L	RASQSIGSWLA	2748	AASSLQS	3442	CQQSYNTPYTF	4136	hFzd9, mFzd9
051S-F01	hFzd9L	RASQSITRWLA	2749	DASTLQS	3443	CQQSYSTPLTF	4137	hFzd9, mFzd9
051S-G01	hFzd9L	KSSQSVLYSSNN KNYLA	2750	WASTRQS	3444	CQQYYGVPLTF	4138	hFzd9, mFzd9
051S-H01	hFzd9L	RSSQSLLHSNGY NYLD	2751	LGSNRAS	3445	CMQALQPPFTF	4139	hFzd9, mFzd9
051S-A02	hFzd9L	RSSQSLLHSNGY NYLD	2752	QGSRRAP	3446	CMQGTHWPITF	4140	hFzd9, mFzd9
046S-C02	hFzd10L	QASQDISNYLN	2753	SASSLQS	3447	CQQSYSTPFTF	4141	hFzd10L, mFzd10L
046S-E02	hFzd10L	RASQSISRWLA	2754	AASSLQS	3448	CLQDYSYPLTF	4142	hFzd10L, mFzd10L
046S-H02	hFzd10L	RSSQSLLHSNGY NYLD	2755	AASSLQS	3449	CMQGLQTPYTF	4143	hFzd10L, mFzd10L
046S-A03	hFzd10L	RASQSISSYLN	2756	ATATLNS	3450	CQQGYNIPFTF	4144	hFzd10L, mFzd10L
046S-F03	hFzd10L	RSSQSLLHSNGY NYLD	2757	DASNLEA	3451	CMQTTHWPWT F	4145	hFzd10L, mFzd10L
046S-B04	hFzd10L	RSSQSLLHSNGY NYLD	2758	DASSLES	3452	CMQGLQTPWAF	4146	hFzd10L, mFzd10L
046S-A05	hFzd10L	RASQSISTWLA	2759	AASTLQS	3453	CQQAYGFPPTF	4147	hFzd10L, mFzd10L
046S-G01	hFzd10L	RASQGISSYLA	2760	GASTLHS	3454	CQQSYNSPPTF	4148	hFzd10L
046S-A02	hFzd10L	RSSQSLLHSNGY NYLD	2761	KASSLES	3455	CMQGLEAPITF	4149	hFzd10L
046S-B03	hFzd10L	RSSQSLLHSNGY NYLD	2762	DASNLGT	3456	CMQALQTPPTF	4150	hFzd10L
046S-A04	hFzd10L	RSSQSLLHSNGY NYLD	2763	LGSNRAS	3457	CMQALQSPITF	4151	hFzd10L
046S-C05	hFzd10L	RASQSISSWLA	2764	DASSLQS	3458	CQKYNSAPFTF	4152	hFzd10L, mFzd10L
046S-F05	hFzd10L	RSSQSLLHSNGY NYLD	2765	SASNLQS	3459	CMQALQTPTF	4153	hFzd10L, mFzd10L
046S-A06	hFzd10L	RASQSISSYLN	2766	DASYLEA	3460	CQQSYTTPYTF	4154	hFzd10L
046S-G06	hFzd10L	KSSQSVLYSSNN KNYLA	2767	WASTRES	3461	CQQYYSDPTF	4155	hFzd10L, mFzd10L
046S-D07	hFzd10L	RSSQSLLHSNGY NYLD	2768	LGSSRAS	3462	CMQALQAPPTF	4156	hFzd10L
046S-E07	hFzd10L	RASQGISSYLA	2769	AASSLQS	3463	CQQSYSTPLTF	4157	hFzd10L
046S-F07	hFzd10L	RSSQSLLHSNGY NYLD	2770	LGSDRAS	3464	CMQALQTPITF	4158	hFzd10L, mFzd10L
046S-G07	hFzd10L	RSSQSLLHSNGY NYLD	2771	LGSDRAS	3465	CMQALQTPITF	4159	hFzd10L, mFzd10L
046S-H07	hFzd10L	RASQSISSWLA	2772	DASNLET	3466	CQQYDSYPLTF	4160	hFzd10L, mFzd10L

046S-E08	hFzd10L	RSSQSLLHSNGYNYLD	2773	SGSNRAS	3467	CMQALQTPLTF	4161	hFzd10L, mFzd10L
046S-G08	hFzd10L	KSSQSVLYSSNNKNYLA	2774	WASTRES	3468	CQQYYSDPITF	4162	hFzd10L
046S-A09	hFzd10L	RASQSISSWLA	2775	AASTLQS	3469	CLQDYNYPLTF	4163	hFzd10L
046S-F09	hFzd10L	QASQDISNYLN	2776	GASSLQS	3470	CQQSYSSPTTF	4164	hFzd10L
046S-D10	hFzd10L	RSSQSLLHSNGYNYLD	2777	LGSNRAS	3471	CMQGTHWPVTF	4165	hFzd10L, mFzd10L
046S-F10	hFzd10L	RASQSISSWLA	2778	AASSLQS	3472	CQQANNYPITF	4166	hFzd10L, mFzd10L
046S-G10	hFzd10L	RASQSISRWLA	2779	GASTRAT	3473	CQQYDSYPITF	4167	hFzd10L, mFzd10L
046S-D11	hFzd10L	RASQGISNYLA	2780	AASTLQS	3474	CQQGYSTPLTF	4168	hFzd10L, mFzd10L
046S-F11	hFzd10L	RASQSISSYLN	2781	DASNLET	3475	CQQSYSIPITF	4169	hFzd10L, mFzd10L
046S-G11	hFzd10L	RSSQSLLHSNGYNYLD	2782	LGSNRAS	3476	CMQALQTPLTF	4170	hFzd10L
046S-E12	hFzd10L	RSSQSLLHSNGYNYLD	2783	LGSNRAS	3477	CMQALETPTF	4171	hFzd10L, mFzd10L
046S-G12	hFzd10L	RSSQSLLHSNGYNYLD	2784	LGSDRAS	3478	CLQGTHWPPTF	4172	hFzd10L, mFzd10L
047S-A01	hFzd10L	RSSQSLLHSNGYNYLD	2785	LGSNRAS	3479	CMQALETPLTF	4173	hFzd10L, mFzd10L
047S-B01	hFzd10L	RSSQSLLHSNGYNYLD	2786	EASTLEH	3480	CMQALQTPYTF	4174	hFzd10L
047S-E01	hFzd10L	RSSQSLLHSNGYNYLD	2787	DASSLET	3481	CMQALQTPPTF	4175	hFzd10L, mFzd10L
047S-A02	hFzd10L	RASQSISSYLN	2788	DASNLET	3482	CQQSYSTPLTF	4176	hFzd10L
047S-C02	hFzd10L	QASQDISNYLN	2789	AASSLQS	3483	CQQYYSTPLTF	4177	hFzd10L
047S-E02	hFzd10L	RASQSISSWLA	2790	DASTLQS	3484	CQQSYDIPITF	4178	hFzd10L, mFzd10L
047S-F02	hFzd10L	RASQGISSWLA	2791	DASNLDA	3485	CQQVNSFPLTF	4179	hFzd10L, mFzd10L
047S-F03	hFzd10L	RSSQSLLHSNGYNYLD	2792	EVSNRAS	3486	CMQALQTPPTF	4180	hFzd10L, mFzd10L
047S-G03	hFzd10L	RASQSISSYLN	2793	AASSLQS	3487	CQQSYNTPLTF	4181	hFzd10L
047S-D04	hFzd10L	RSSQSLLHSNGYNYLD	2794	AASTLES	3488	CMQALQTPITF	4182	hFzd10L, mFzd10L
047S-E04	hFzd10L	RASQGISNYLA	2795	DASNLET	3489	CQQTYTIPLTF	4183	hFzd10L
047S-H04	hFzd10L	RASQSISSWLA	2796	GASNLQS	3490	CQQYAASPSSF	4184	hFzd10L, mFzd10L
047S-C05	hFzd10L	RSSQSLLHSNGYNYLD	2797	AASSLQS	3491	CMQALEAPITF	4185	hFzd10L
047S-E05	hFzd10L	RSSQSLLHSNGYNYLD	2798	SGSNRAS	3492	CMQATHWPWTF	4186	hFzd10L, mFzd10L
047S-F05	hFzd10L	RASQSISSWLA	2799	PGNILQG	3493	CQQTYSTPYTF	4187	hFzd10L, mFzd10L
047S-G05	hFzd10L	RASQSISTYLN	2800	GASNVQS	3494	CQQTYTIPITF	4188	hFzd10L, mFzd10L
047S-C06	hFzd10L	RSSQSLLHSNGYNYLD	2801	EASSLAS	3495	CMQALQTPLTF	4189	hFzd10L, mFzd10L
047S-E06	hFzd10L	RSSQSLLHSNGYNYLD	2802	LGSNRAS	3496	CMQALQTPPTF	4190	hFzd10L, mFzd10L
047S-F06	hFzd10L	RASQSISSWLA	2803	KASTLDS	3497	CQQGYNIPFTF	4191	hFzd10L, mFzd10L
047S-G06	hFzd10L	RASQGISNYLA	2804	AASSLQS	3498	CLQHKKYPLTF	4192	hFzd10L, mFzd10L
047S-A07	hFzd10L	RSSQSLLHSNGYNYLD	2805	LGSNRAS	3499	CMQALQTPLTF	4193	hFzd10L, mFzd10L
047S-B07	hFzd10L	RSSQSLLHSNGYNYLD	2806	LGSNRAS	3500	CMQGLQSPVTF	4194	hFzd10L
047S-C07	hFzd10L	RASQSISTYLN	2807	AASTLHS	3501	CQQANSFPLTF	4195	hFzd10L, mFzd10L

047S-F07	hFzd10L	QASQDISNYLN	2808	DASNLET	3502	CQQSYNTPYTF	4196	hFzd10L, mFzd10L
047S-G07	hFzd10L	RASQGISSWLA	2809	DVSTLQS	3503	CQQGYSTPLTF	4197	hFzd10L
047S-H07	hFzd10L	RSSQSLLHSNGY NYLD	2810	LGSNRAS	3504	CMQALQTPLTF	4198	hFzd10L, mFzd10L
047S-A08	hFzd10L	RASQSISSWLA	2811	GASNLQS	3505	CQHYAASPSSF	4199	hFzd10L, mFzd10L
047S-C08	hFzd10L	KSSQSVLYSSNN KNYLA	2812	WASTRES	3506	CQQYYDTPYTF	4200	hFzd10L, mFzd10L
047S-D08	hFzd10L	RSSQSLLHSNGY NYLD	2813	LGSNRAS	3507	CMQALQVPLTF	4201	hFzd10L, mFzd10L
047S-B11	hFzd10L	RSSQSLLHSNGY NYLD	2814	SGSNRAS	3508	CMQALQTPFTF	4202	hFzd10L, mFzd10L
047S-E12	hFzd10L	RSSQSLLHSNGY NYLD	2815	LGSNRAS	3509	CMQGSHWPLTF	4203	hFzd10L, mFzd10L

EXAMPLE 2

IG CONSTRUCTION AND BINDING AFFINITY DETERMINATION

Certain VL and VH clones from Table 1 were PCR amplified from the phage clone and sub-cloned into pcDNA3.1 based mammalian expression vectors (Invitrogen/ThermoFisher) of human kappa or lambda light chain and human IgG1 heavy chain, respectively. Candidate IgGs were purified using Protein A affinity resin. The candidate library was captured on an anti-FC lawn. The capture lawn was prepared by direct amine coupling goat anti-human IgG Fc (Southern Biotech #2048-01) at 8000 RU on a HC200M Carterra sensor chip (Carterra 4297). Capture levels were at least 600 RU for each candidate IgG. Binding to all target peptides was measured at 25° by injecting a concentration series of each peptide in 1xPBST + 0.5 mg/mL BSA (TEKnova P1192, VWR V0332). All peptides were injected at 4.12 nM, 12.3 nM, 37 nM, 111 nM, 333 nM, and 1000 nM. Two blank injections were run between each peptide concentration series. Each injection started with a one minute baseline determination, followed by a five minute association phase where peptides were injected, and finished with a 10 minute dissociation phase. Binding data was analyzed using NextGenKIT (Carterra). Blank injections and reference locations were subtracted from all runs prior to fitting a 1:1 binding model to the data. Table 3 shows the results following analysis on the Carterra LSA microfluidic surface plasmon resonance detection instrument (Carterra, Salt Lake City, UT). Interactions with an R_{max} less than 15 RU or weaker than 5 μM were considered non-binders.

Table 3. Binding of monospecific Fzd clones.

		Fzd1	Fzd2	Fzd3	Fzd4	Fzd5	Fzd6	Fzd7	Fzd8	Fzd9	Fzd10
Name	Target	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo	Hu/ Mo

033S-A01	Fzd1L	* / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-B01	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-C01	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-D01	Fzd1L	* / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-E01	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-H01	Fzd1L	* / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-B02	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-C02	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-D02	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-E02	Fzd1L	*** / ***	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-F02	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-G02	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-H03	Fzd1L	** / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-A03	Fzd1L	*** / ***	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-B03	Fzd1L	**** / ****	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-C03	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-D03	Fzd1L	* / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
034S-C01	Fzd1L	** / *	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
033S-E03	Fzd1L	*** / ***	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
034S-F01	Fzd1L	* / *	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
034S-H01	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
037S-H01	Fzd1L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
48SH1	Fzd2L	- / -	** / ***	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
031S-G01	Fzd2L	- / -	** / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
037S-G02	Fzd2L	- / -	** / **	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
037S-D03	Fzd2L	- / -	** / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
037S-F05	Fzd2L	- / -	- / **	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
49SC1	Fzd2L	- / -	*** / ***	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
49SD1	Fzd2L	- / -	** / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SE1	Fzd3L	- / -	- / -	** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SA2	Fzd3L	- / -	- / -	*** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SC2	Fzd3L	- / -	- / -	** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SD2	Fzd3L	- / -	- / -	** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SE2	Fzd3L	- / -	- / -	** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SF3	Fzd3L	- / -	- / -	*** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SG3	Fzd3L	- / -	- / -	*** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SA10	Fzd3L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
45SE4	Fzd3L	- / -	- / -	- / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SF1	Fzd3L	- / -	- / -	** / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SD3	Fzd3L	- / -	- / -	** / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
44SG9	Fzd3L	- / -	- / -	*** / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
39SC12	Fzd4L	- / -	- / -	- / -	- / **	- / -	- / -	- / -	NT / -	- / -	- / -
39SF11	Fzd4L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
40SF1	Fzd4L	* / *	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -

40SE4	Fzd4L	**** / ****	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
40SG2	Fzd4L	- / -	- / -	- / -	* / -	- / -	- / -	- / -	NT / -	- / -	- / -
40SF4	Fzd4L	- / *	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
38SG1	Fzd4L	- / -	- / -	- / -	*** / ***	- / -	- / -	- / -	NT / -	- / -	- / -
38SH3	Fzd4L	- / -	- / -	- / -	** / **	- / -	- / -	- / -	NT / -	- / -	- / -
36SB1	Fzd5L	- / -	- / -	- / -	- / -	* / -	- / -	- / -	NT / -	- / -	- / -
36SC1	Fzd5L	- / -	- / -	- / **	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
36SF4	Fzd5L	- / -	- / -	- / -	- / -	*** / -	- / -	- / -	NT / -	- / -	- / -
36SB4	Fzd5L	- / -	- / -	- / -	- / -	** / -	- / -	- / -	NT / -	- / -	- / -
36SG4	Fzd5L	- / -	- / -	- / -	- / -	** / -	- / -	- / -	NT / -	- / -	- / -
35SE1	Fzd5L	- / -	- / -	- / -	- / -	** / -	- / -	- / -	NT / -	- / -	- / -
41SG5	Fzd6L	*** / ***	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
41SA10	Fzd6L	- / -	- / -	- / -	- / -	- / -	** / -	- / -	NT / -	- / -	- / -
41SB3	Fzd6L	- / -	- / -	- / -	- / -	- / -	** / -	- / -	NT / -	- / -	- / -
41SB5	Fzd6L	- / -	- / -	- / -	- / -	- / -	*** / **	- / -	NT / -	- / -	- / -
41SB1	Fzd6L	- / -	- / -	- / -	- / -	- / -	- / *	- / -	NT / -	- / -	- / -
40SB12	Fzd6L	- / -	- / -	- / -	- / -	- / -	* / *	- / -	NT / -	- / -	- / -
41SB5	Fzd6L	- / -	- / -	- / -	- / -	- / -	** / **	- / -	NT / -	- / -	- / -
40SB10	Fzd6L	- / -	- / -	- / -	- / -	- / -	** / **	- / -	NT / -	- / -	- / -
40SG10	Fzd6L	- / -	- / -	- / -	- / -	- / -	- / **	- / -	NT / -	- / -	- / -
40SG7	Fzd6L	- / -	- / -	- / *	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
49SB2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	*** / -	NT / -	- / -	- / -
49SD2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	*** / **	NT / -	- / -	- / -
49SE2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / **	NT / -	- / -	- / -
49SH2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	*** / ***	NT / -	- / -	- / -
49SA3	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / **	NT / -	- / -	- / -
49SD3	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / ***	NT / -	- / -	- / -
49SG3	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / -	NT / -	- / -	- / -
49SA4	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / **	NT / -	- / -	- / -
32SH2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / **	NT / -	- / -	- / -
32SF2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	** / -	NT / -	- / -	- / -
32SD2	Fzd7L	- / -	- / -	- / -	- / -	- / -	- / -	*** / ***	NT / -	- / -	- / -
50SD10	Fzd9L	- / -	- / -	** / *	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
50SA11	Fzd9L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	* / **	- / -
50SG11	Fzd9L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	** / **	- / -
46SF1	Fzd10L	* / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
46SB2	Fzd10L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
46SC2	Fzd10L	** / **	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
46SE2	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / ***
46SG2	Fzd10L	- / *	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	- / -
46SH4	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / *
047S-D05	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	*** / **
46SF2	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / **
46SF3	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / -

46SF4	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / **
47SG6	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / -
46SB1	Fzd10L	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / -	- / -	** / **

NT = Not Tested;

-- = No Binding;

* = KD > 1 uM; * = KD > 1 uM;

** = 1 uM > KD > 100 nM;

*** = 100 nM > KD > 10 nM;

**** = 10 nM > KD

EXAMPLE 3

EXPRESSION AND PURIFICATION OF FAB BINDER

Plasmids expressing light-chain and heavy-chain (with hexa-histidine tag at its C-terminus) of a Fab binder against mouse Fzd8 hinge region (15G4-4) or human Fzd8 CRD (027S-E5) was co-transfected for co-expression in Expi293 cells, following the standard protocols from the manufacturer (ThermoFisher). After 4 days of continuous cell growth, media were harvested by centrifugation, and bound to Complete-His resin (2.5mL per 1L culture; Roche) pre-equilibrated in PBS, and eluted under gravity-flow using 250mM imidazole in PBS. Elutions containing the Fab binder were concentrated to ~5mL, and further polished on a HiLoad 16/600 Superdex 200 pg column (GE Life Sciences) column pre-equilibrated with HBS. Fractions near main peak were further analyzed by SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE) to confirm the content. SDS-PAGE was performed using Tris-HCl 4-15% gel (Bio-Rad, Hercules, CA) under both reducing and non-reducing conditions. The samples were prepared in Laemmli sample buffer and heated at 100°C for 5 min. Fractions containing 15G4-4 were concentrated to ~3mg/mL and frozen in the presence of 10% glycerol for storage at -80°C until further use. Protein concentrations were determined using a NanoDrop Spectrophotometer (Thermo Scientific) by the direct UV A280 method. The relationship of absorbance to protein concentration is linear based on Beer-Lamber equation, $A = \varepsilon l c$; A is the absorbance value, ε is the wavelength- dependent

extinction coefficient, l is the path length in centimeters, and c is the protein concentration. The extinction coefficients of all produced proteins were estimated by their amino acid sequences.

EXAMPLE 4

FAB BINDING AFFINITIES

Binding kinetics of clone 027S-E5 specific to the Fzd cysteine rich domain (CRD) of human Fzd8, was determined by bio-layer interferometry (BLI) using Octet Red 96 (PALL ForteBio, Fremont, CA) instruments at 30° C, 1000 rpm with streptavidin (SA) biosensors. C-terminal biotinylated Fzd CRD recombinant protein was diluted to 20 nM in the running buffer (PBS, 0.05% Tween-20, 0.5% BSA, pH 7.2) and captured to the SA biosensor until coupling length reached 0.2 nm. Following capture of the Fzd CRD, the SA biosensor with captured biotinylated-Fzd CRD was dipped into wells containing the relevant antibody fragment at 7 different concentrations (0, 1.37, 4.12, 12.4, 37, 111.1, 333.3, 1000 nM) in running buffer, plus a well with only running buffer as a reference channel. K_D was determined by global fitting, 1:1 binding model according to manufacturer recommended settings.

Candidate Fab (15G4-4) was purified by nickel affinity resin. Biotinylated target peptides were captured on a NeutrAvidin lawn. The capture lawn was prepared by direct amine coupling NeutrAvidin (ThermoFisher 31000) to a CMDP Carterra sensor chip. Binding was measured by injecting the Fabs at 4.12 nM, 12.3 nM, 37 nM, 111 nM, 333 nM, and 1000 nM. Each injection started with a one minute baseline determination, followed by a five minute association phase where peptides were injected, and finished with a 10 minute dissociation phase. Binding data was analyzed using NextGenKIT (Carterra). Blank injections and reference locations were subtracted from all runs prior to fitting a 1:1 binding model to the data. Interactions with an R_{max} less than 15 RU or weaker than 5 μM were considered non-binders. Table 4 provides the binding affinities for 15G4-4 and 027S-E5.

Table 4: Binding Affinity of FZD8 Fab clones

		Fzd1	Fzd2	Fzd3	Fzd4	Fzd5	Fzd6	Fzd7	Fzd8	Fzd9	Fzd10
Name	Target	H/M	H/M	H/M	H/M	H/M	H/M	H/M	H/M	H/M	H/M
15G4-4	mFzd8	- / -	- / -	- / -	- / -	- / -	- / -	- / -	NT / **	- / -	- / -

027S-E5	hFzd8 (CRD)	-/-	-/-	-/-	-/-	-/-	-/-	-/-	***/NT	-/-	-/-

NT	Not Tested
-	No Binding
*	KD $\geq$ 1 uM
**	1 uM > KD $\geq$ 100 nM
***	100 nM > KD $\geq$ 10 nM
****	10 nM > KD

EXAMPLE 5

CRYSTAL STRUCTURES OF ANTI-FZD ANTIBODY FRAGMENTS BOUND TO FZD EXTRA-CELLULAR DOMAINS

Fzds are a class of GPCRs in which an extra-cellular Cys-rich domain (CRD) is connected to its 7-transmemberane helical domain and cytoplasmic tail through a linker region. Fzds have either one or two predicted -NxS/T- glycosylation motifs within their extra-cellular domain. To enable high-resolution structures, Fzds extra-cellular domains that contain two glycosylation motifs were truncated before second predicted -NxS/T- glycosylation motifs resulting constructs named CRD-Xtal. Sequence of each of 10 Fzd CRD-Xtal containing an eight-Histidine motif at their C-terminus are as follows:

hFzd8_Q9H461_28-153 (SEQ ID NO: 11)

ASAKELACQEITVPLCKGIGYNYTYMPNQFNHDTQDEAGLEVHQFWPLVEIQCSPD LKFFLCSMYTPICLEDYKKPLPPCRSVCERAKAGCAPLMRQYGFAWPDRMRCDRL PEQGNPDTLCMDYNRHHHHHHHH

EXAMPLE 6

EXPRESSION AND PURIFICATION OF FZD8-CRD PROTEIN

FreeStyle™ 293-F Cells (Thermofisher) stably expressing all Fzd8-CRD was created using lenti-viral technology. For large-scale expression, a frozen vial FreeStyle™ 293-F Cells expressing Fzd8-CRD was thawed into 20mL of FreeStyle (Thermofisher) media in the presence of 10 U penicillin and 10ug of streptomycin (Lonza) per mL. Cells were expended on alternative days, until density of ~3.0x10^6 cell/mL was reached at desired volumes, typically 5 to 10L. At this stage, cells were

allowed to grow continuously to higher density and, media was harvested by centrifugation at a viability of ~70%. Fzd8-CRD protein was purified from media by incubation with Ni-NTA resin (1mL per L of culture; Qiagen) pre-equilibrated in HBS (20mM HEPES pH 7.4, 150mM NaCl), and washed sequentially with 10 CV (column volume) of HBS, HBS + 0.5mM EDTA, HBS, HBS + 500mM sodium chloride, and HBS. Fzd8-CRD was eluted with 10 CV of 500mM imidazole in HBS using a gravity-flow glass-coumn. Ni-NTA eluates were concentrated to 5mL, and further polished on a HiLoad 16/600 Superdex 200 pg column (GE Life Sciences) pre-equilibrated with HBS. Fractions near the main peak was further analyzed by SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE; Tris-HCl 4-15% gel Bio-Rad, Hercules, CA) to confirm the content. The samples were prepared in Laemmli sample buffer and heated at 100ºC for 5 min. Fractions containing Fzd8-CRD were concentrated to ~3mg/mL and frozen in the presence of 10% glycerol for storage at -80°C until further use. Protein concentrations were determined using a NanoDrop Spectrophotometer (Thermo Scientific) by the direct UV A280 method. The relationship of absorbance to protein concentration is linear based on Beer-Lamber equation, $A = \varepsilon l c$; A is the absorbance value, ε is the wavelength- dependent extinction coefficient, l is the path length in centimeters, and c is the protein concentration. The extinction coefficients of all produced proteins were estimated by their amino acid sequences.

EXAMPLE 7

EXPRESSION AND PURIFICATION OF FAB-DOMAIN OF ANTI-FZD8 ANTI-BODY 27SE5

Plasmids expressing light-chain and heavy-chain (with hexa-histidine tag at its C-terminus) of Fab-domain of 27SE5 were transfected for expression in Expi293 cells (ThermoFisher USA), typically at 1000mL scale, using FectoPro transfection agent following standard protocols from the manufacturer (Polyplus Transfection NY USA). After 4 days of continuous cell growth, media were harvested by centrifugation, and bound to Complete-His resin (2.0mL per 1L culture; Roche) pre-equilibrated in 50 mM sodium di-hyrogen phosphate pH 8.0, 300 mM NaCl and eluted under gravity-flow using 250mM imidazole in the same buffer. Elutions containing Fab binders were concentrated to ~5mL, and further polished on a HiLoad 16/600 Superdex 200 pg column (GE Life Sciences) column pre-equilibrated with

HBS. Fractions near main peak was further analyzed by SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE; Tris-HCl 4-15% gel from Bio-Rad, Hercules, CA) to confirm the content. The samples were prepared in Laemmli sample buffer and heated at 100ºC for 5 min. Fractions containing 27SE5 Fab were concentrated to ~5 mg/mL and frozen in the presence of 10% glycerol for storage at -80C until further use. Protein concentrations were determined using a NanoDrop Spectrophotometer (Thermo Scientific) by the direct UV A280 method. The relationship of absorbance to protein concentration is linear based on Beer-Lamber equation, $A = \varepsilon l c$; A is the absorbance value, ε is the wavelength- dependent extinction coefficient, l is the path length in centimeters, and c is the protein concentration. The extinction coefficients of all produced proteins were estimated by their amino acid sequences.

The sequences of the VH and VL chains of 027S-E5 Fab were as follows:

027SE5_SZC02378_VH (SEQ ID NO: 30)
QVQLEQSGAEVKKPGASVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGMINPS
GGSTTYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARQAGLHCSSTSC
YLGNWFDPWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCGSGSGHHHHHH

027SE5_SZC02377_VL (SEQ ID NO: 31)
DIQMTQSPSSLSASVGDRVTITCRASQGITKSLAWYQQKPGKAPKLLIYAASNLATG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNTFPITFGQGTRLEIKRTVAAPS
VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK
DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

EXAMPLE 8

HuFzd8-CRD:27SE5 COMPLEX FORMATION, CRYSTALLIZATION, AND STRUCTURE DETERMINATION

Purified HuFzd8-CRD and 27SE5 Fab were mixed at 1.1:1 molar ratio (little excess of the HuFzd8-CRD) and incubated with carboxy-peptidase A and B at a w/w ratio of 100:1 for over-night at 4°C. Complex formation was confirmed by observation of a single-major peak on SuperdexS200 Increase (10/300 GL) column pre-equilibrated in HBS. Fractions containing HuFzd8-CRD:27SE5 complex were further

checked by SDS-PAGE and concentrated to 36.5 mg/mL for crystallization screens. Initial crystallization screen, using commercially available MCSG1, MCSG2, MCSG3, MCSG4 (Molecular Dimensions USA), PEGs I, and PEGs II (Qiagen USA) screen, and optimization by grid-screens or microseed matrix screen (see, e.g., D'Arcy A, et al. (2014) *Acta Cryst*. F70, 1117-1126) were performed using Mosquito (TTP LabTech) liquid handler and equilibrated at 18°C inside an EchoTherm incubator (Torrey Pines Scientific USA). 96-well plate crystal screening experiments were periodically monitored manually via a DiscoveryV20 stereomicroscope (Zeiss USA), and crystals were frozen for data collection by plunging into liquid nitrogen in the presence of various cryo-protectants (typically 15 to 30% v/v of glycerol or ethyleneglycol). X-ray diffraction datasets were collected at the Berkeley Center for Structural Biology at the Advanced Light Source (ALS), Berkeley CA, and processed with XDS (Kabsch W. (2010) *Acta Cryst*. D66:125-132), and xdsme (see, e.g., Legrand P. (2017) https://github.com/legrandp/xdsme DOI 10.5281/zenodo.837885) programs. Structure of HuFzd8-CRD:27SE5 complex was determined by molecular replacement method using Phaser (Phaser crystallographic software), using previously determined structures of HuFzd8-CRD and variable and constant domains of an unrelated Fab at Surrozen Inc, followed by refinement and validation by MolProbity as implemented in Phenix (see, e.g., P.D. Adams, et al. (2010) *Acta Cryst* D66:213-221) and MolProbity (see, e.g., Chen VB, et al. (2010) Acta Cryst. D66:12-21). Crystallography models were manually inspected and built using (see,.e.g.,Emsleym P (2010) *Acta Cryst*.D66:486-501). Analyses of refined crystal structures, and image creations were performed using MOE (CCG) and PyMol (Schrodinger).

EXAMPLE 9

STRUCTURE OF HUFZD8-CRD:27SE5-FAB COMPLEX

Diffraction quality crystals of HuFzd8-CRD:27SE5 complex (concentration = 36.5 mg/mL) grew in a crystallization condition containing 1.2 M sodium chloride and 20 % (w/v) PEG3350. Crystal was cryo-protected using 16% glycerol in the well-solution. HuFzd8-CRD:27SE5 complex crystallized in the $C222_1$ space group (a = 60.63 Å, b = 93.23 Å, c = 272.437 Å) with one complex molecules per asymmetric

unit. Structure of HuFzd8-CRD:27SE5 complex was determined at a resolution of 1.95 Å and refined to R_{cryst} and R_{free} factors of 22.3% and 27.2%, respectively.

Overall structure of HuFzd8-CRD:27SE5 complex is shown in Figures 1A and 1B, which revealed that the 27SE5 binds opposite to the lipid binding site as observed in the complex of Fzd8:Wnt8a complex (PDB Code: 4F0A; Janda CY et al. (2012) *Science* 337: 59-6) and recognizes the C-terminal region of Fzd8. Electron density maps revealed a di-sulfide bond within CDR-H3 between Cys104-Cys109, which interacts with the Asn49, a glycosylation-site on human Fzd8.

Structure of the complex allowed the identification of the epitope on human Fzd8 as well as residue interactions (paratopes) on 027S-E5, as summarized in Table 5. NAG1 (N-acetyl-D-glucosamine) was attached Asn49 of Fzd8.

Table 5: Interaction Residues for 027S-E05:hFzd8 binding

	≤ 5Å	>5Å and < 8Å
Fzd 8 Residues	Gly47, Tyr48, Asn49, Tyr50, Ile95, Cys96, Leu97, Glu98, Asp99, Tyr100, Lys101, Lys102, Leu104, Gln141, Gly142, Asn143, Pro144, Leu147, Cys148, Met149, Asp150, and Tyr151.	Cys35, Gln36, Glu37, Ile38, Thr51, Phe86, Pro105, Cys107, Ser109, Val110, Arg113, Glu140, Asp145, Thr146, and Asn142
027S-E5 heavy chain residues	Asn52, Pro53, Ser54, Ser57, Thr58, Thr59, Leu102, Cys104, Ser105, Ser106, Thr107, Ser108, Cys109, Tyr110, Leu111, Gly112, and Trp114	Ser30, Ala33, Trp47, Met50, Ile51, Gly55, Gly56, Tyr60, Ala61, Gln62, Gln65, Gly101, His103, and Asn113
027S-E05 light chain residues	Ile29, Thr30, Lys31, Ser32, Ala50, Ser52, Asn53, Tyr91, Asn92, Thr93, and Phe94	Ile2, Gln27, Gly28, Leu33, Ala34, Try49, Ala51, Ser67, Phe71, Gln90, and Pro95

EXAMPLE 10

MONOSPECIFIC WNT SURROGATE MOLECULES

Active Wnt surrogate molecules were generated comprising various combinations of Fzd binders that bind the Fzd receptor hinge region (see FIG. 1) and LRP binders (see, e.g., WO2019126398, which is incorporated herein, by reference). Three Fab fragment binders that bound to the hinge region of Fzd1 (033S-B03, 033S-D02, and 033S-E02; VLs - SEQ ID NOs:14, 16, and 18; VHs – SEQ ID NOs: 15, 17, and 19) and one Fab fragment binder that bound Fzd2 (031S-B02; VL - SEQ ID NO: 20; VH – SEQ ID NO: 21) were used to demonstrate that binders to the Fzd hinge region yield active Wnt surrogate molecules.

Recombinant Fab fragments of these antibodies were produced from Expi293F cells (Thermo Fisher Scientific, Waltham, MA) via transient transfection. The Fabs were purified from the culture media with Nickel resin and further polished with size exclusion chromatography (SEC).

The anti-FZD1 hinge and anti-FZD2 hinge antibodies were cloned into human IgG1 framework with LALA-PG mutations in Fc to reduce effector functions. LRP5 binder #3 (008S-D01; SEQ ID NO: 12) or LRP5/6 binder #36 (013S-D05; SEQ ID NO: 13) were cloned in frame to the N-termini of the light chains of respective antibodies as depicted in FIG. 2.

EXAMPLE 11

BINDING KINETICS OF HINGE REGION-SPECIFIC WNT SURROGATE MOLECULES

Binding kinetics of monospecific Fzd binders to either (CRD) or the extracellular hinge region (hinge) was determined by bio-layer interferometry (BLI) using Octet Red 96 (PALL ForteBio, Fremont, CA) instruments at 30° C, 1000 rpm with streptavidin (SA) biosensors. N-terminal biotinylated Fzd1 or Fzd2 CRD and Fzd1 or Fzd 2 hinge proteins were captured on the SA biosensor. Following capture of biotinylated-Fzd1 or Fzd2, the SA biosensor with captured biotinylated-Fzd7 was dipped into wells containing the relevant antibodies at 7 different concentrations in running buffer plus a well with only running buffer as a reference channel. KD was determined by global fitting. As shown in

FIGS. 4A-4H these antibody fusion proteins only bound to either Fzd1 or Fzd2 protein with the hinge region, and not to the CRD domains alone.

EXAMPLE 12

IN VITRO ACTIVITY OF HINGE REGION-SPECIFIC WNT SURROGATE MOLECULES

The ability of Wnt surrogates comprising antibodies that bind the Fzd1 or Fzd2 hinge regions to activate Wnt signaling was assessed in the 293 STF cell line overexpressing either Fzd1 or Fzd2, where the β-Catenin luciferase reporter plasmid Super TOP Flash (STF) was stably integrated. For the Luciferase reporter assays, in each 96 well plate, 1 million cells were seeded, IWP2 (a wnt signaling inhibitor) was added at 3 μM final concentration. 26 hours after seeding, compounds were added to the 96 well plates with triplicates and 10-fold series dilution from100nM, and the highest concentration is 500nM. 18 hours later, cells were lysed with 100 μl lysis buffer. From the above lysed cells, 20 ul samples were transferred to opaque 96- well plates. Toward each well, 10 μl of luciferase substrate was added. The plate was immediately placed in Molecular Device Lum96 plate reader and luciferase luminescence signals were collected. Data were processed with Prism7. These antibodies activated Wnt signaling as judged by the induction of luciferase reporter in these cells with either Fzd1 or Fzd 2 overexpression in the present of 20 nM R-spondin 2 (RPSO). These results demonstrate that Fzd hinge binding antibodies when assembled with LRP binders can induce Wnt signaling activation.

The recombinant appended IgG proteins were prepared by transfection of respective expression vectors into Expi293F cells (Thermo Fisher Scientific, Waltham, MA) according to the manufacturer's instructions. Briefly, four days after the transfection, cell culture medium was collected after spinning down the cell pellet. The media was incubated with Protein A resin (REPLIGEN, Waltham, MA) for collecting proteins containing human IgG-Fc portion. Proteins were eluted with 10 mM glycine, pH 3.5 from Protein A resin. Subsequently, the protein elutes were fractionated and further purified by size-exclusion chromatography (SEC). SEC was performed by a fast protein liquid chromatography using a Superdex 200 Increase 10/300 GL (GE Healthcare, Pittsburgh, PA) in HBS buffer (10 mM HEPES, 150 mM NaCl, pH7.4). The peak

fractions were analyzed by SDS-Polyacrylamide Gel Electrophoresis (SDS-PAGE) to confirm the content. Figures 5A and 5B demonstrate that the monospecific Wnt surrogate molecules can activate Wnt signaling.

Table 6A: Sequences of Wnt Surrogate Components

Clone ID	Antigen	VL/VH	Sequence
013S-D05 (#36)	LRP5/6	VH	QVKLEESGGGLVQAGGSLRLSCAASGRIFSIYDMGWFRQAPGKE EFVSGIRWSGGTSYADSVKGRFTISKDNAKNTIYLQMNNLKAEDT VYYCGSRGYWGQGTLVTVSS (SEQ ID NO: 12)
008S-D01 (#3)	LRP5	VH	DVQLVESGGGLVQPGGSLRLSCTSSANINSIETLGWYRQAPGK QRELIANMRGGGYMKYAGSLKGRFTMSTESAKNTMYLQMNSL KPEDTAVYYCYVKLRDDDYVYRGQGTQVTVSS (SEQ ID NO: 13)
033S-B03	Fzd1	VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSIRASGVPDRFSGSGSGTDFTLKISRVEAED VGVYYCMQALQTPLTFGGGTKVEIK (SEQ ID NO: 14)
033S-B03	Fzd1	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTGQYMHWVRQAP GQGLEWMGGIIPIFGTAHYPQKFQGRVTITADESTSTAYMELSS LRSEDTAVYYCARRSVAAGTPFTDYWGQGTLVTVSS (SEQ ID NO: 15)
033S-D02	Fzd1	VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSHRASGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQGLQTPITFGGGTKVEIK (SEQ ID NO: 16)
033S-D02	Fzd1	VH	QVQLVQSGAEVKKPGSSVKVSCKASGITFTSSAVHWVRQAPG QGLEWLGIINPSGGSTSYAQKFQGRVTITADESTSTAYMELSSL RSEDTAVYYCARRMVYAPYKDVWGKGTMVTVSS (SEQ ID NO: 17)
033S-E02	Fzd1	VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQ KPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAE DVGVYYCMQALQTPLTFGGGTKVEIK (SEQ ID NO: 18)
033S-E02	Fzd1	VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFTSYAISWVRQAPG QGLEWMGMINPSGGRTTYAQKFQGRVTITADESTSTAYMKLS SLRSEDTAVYYCAIRTIFGVVIDYWGQGTLVTVSS (SEQ ID NO: 19)
031S-B02	Fzd2	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSGSYLAWYQQKPG QAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVY YCQQYGSSPLTFGQGTKVEIK (SEQ ID NO: 20)
031S-B02	Fzd2	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMSWVRQAP GKGLEWVSAIGGSGANAYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAVYYCVRDTNWAFDLWGQGT MVTVSS (SEQ ID NO: 21)

Table 6B: Monspecific Wnt Surrogate Constructs

Lrp VHH or sdAb = italics

anti-Fzd light chain = underline

anti-Fzd heavy chain = bold

Construct	SID NO:	Sequence
033S-B03-36 LC	22	MDMRVPAQLLGLLLLWLRGARC*QVKLEESGGGLVQAGGSLRLSCA ASGRIFSIYDMGWFRQAPGKEREFVSGIRWSGGTSYADSVKGRFTI SKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS*GGS GSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSIRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVY YCMQALQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
033S-B03-36 HC	23	MDMRVPAQLLGLLLLWLRGARC**QVQLVQSGAEVKKPGSSVKVSC KASGYTFTGQYMHWVRQAPGQGLEWMGGIIPIFGTAHYPQKFQG RVTITADESTSTAYMELSSLRSEDTAVYYCARRSVAAGTPFTDYW GQGTLVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFP PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKT ISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK*
033S-E02-36 LC	24	MDMRVPAQLLGLLLLWLRGARC*QVKLEESGGGLVQAGGSLRLSCA ASGRIFSIYDMGWFRQAPGKEREFVSGIRWSGGTSYADSVKGRFTI SKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS*GGS GSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQK PGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGV YYCMQALQTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
033S-E02-36 HC	25	MDMRVPAQLLGLLLLWLRGARC**QVQLVQSGAEVKKPGSSVKVSC KASGGTFTSYAISWVRQAPGQGLEWMGMINPSGGRTTYAQKFQG RVTITADESTSTAYMKLSSLRSEDTAVYYCAIRTIFGVVIDYWGQGT LVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKA KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGK*
033S-D02-3 LC	26	MDMRVPAQLLGLLLLWLRGARC*DVQLVESGGGLVQPGGSLRLSCT SSANINSIETLGWYRQAPGKQRELIANMRGGGYMKYAGSLKGRFT MSTESAKNTMYLQMNSLKPEDTAVYYCYVKLRDDDYVYRGQGTQ VTVSS*GGSGSDIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYN YLDWYLQKPGQSPQLLIYLGSHRASGVPDRFSGSGSGTDFTLKISR VEAEDVGVYYCMQGLQTPITFGGGTKVEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*

033S-D02-3 HC	27	MDMRVPAQLLGLLLLWLRGARC**QVQLVQSGAEVKKPGSSVKVSC KASGITFTSSAVHWVRQAPGQGLEWLGIINPSGGSTSYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYCARRMVYAPYKDVWGKG TMVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISK AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPGK*
031S-B02-36 LC	28	MDMRVPAQLLGLLLLWLRGARC*QVKLEESGGGLVQAGGSLRLSCA ASGRIFSIYDMGWFRQAPGKEREFVSGIRWSGGTSYADSVKGRFTI SKDNAKNTIYLQMNNLKAEDTAVYYCGSRGYWGQGTLVTVSS* GGSGSEIVMTQSPATLSVSPGERATLSCRASQSVSGSYLAWYQQK PGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVY YCQQYGSSPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC*
031S-B02-36 HC	29	MDMRVPAQLLGLLLLWLRGARC**EVQLLESGGGLVQPGGSLRLSC AASGFTFSSYWMSWVRQAPGKGLEWVSAIGGSGANAYYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCVRDTNWAFDLWGQ GTMVTVSS**ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPK PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK*

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent application, foreign patents, foreign patent application and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, application and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

What is claimed is:

1. An isolated antibody, or an antigen-binding fragment thereof, that binds to one or more Frizzled receptor, comprising a sequence comprising:

(i) CDRH1, CDRH2 and CDRH3 sequences set forth for any of the antibodies of Table 2; and

(ii) CDRL1, CDRL2 and CDRL3 sequences set forth for any of the antibodies of Table 2, or a variant of said antibody, or antigen-binding fragment thereof, comprising one or more amino acid modifications, wherein said variant comprises less than 8 amino acid substitutions in said CDR sequences.

2. The isolated antibody, or antigen-binding fragment thereof, of claim 0, wherein the antibody, or antigen-binding fragment thereof, is humanized.

3. The isolated antibody, or antigen-binding fragment thereof, of any of claims 0-2, wherein the antibody, or antigen-binding fragment thereof, is a single chain antibody, a scFv, a univalent antibody lacking a hinge region, a VHH or sdAb, or a minibody.

4. The isolated antibody, or antigen-binding fragment thereof, of claim 3, wherein the antibody, or antigen-binding fragment thereof, is a VHH or sdAb.

5. The isolated antibody, or antigen-binding fragment thereof, of claim 3, wherein the antibody, or antigen-binding fragment thereof, is a Fab or a Fab' fragment.

6. The isolated antibody, or antigen-binding fragment thereof, of any of claims 1-5, wherein the antibody, or antigen-binding fragment thereof, is a fusion protein.

7. The isolated antibody, or antigen-binding fragment thereof, of claim 6, wherein the antibody, or antigen-binding fragment thereof, is fused to a polypeptide sequence that binds LRP5 or LRP6.

8. The isolated antibody, or antigen-binding fragment thereof, of claim 7, wherein the polypeptide sequence that binds LRP5 or LRP6 is an antibody, or an antigen-binding fragment thereof, that binds to LRP5 or LRP6.

9. The isolated antibody, or antigen-binding fragment thereof, of any of claims 1-8, wherein the antibody, or antigen-binding fragment thereof, binds to one of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

10. The isolated antibody or antigen binding fragment of claim 9, having:

a) a variable light chain sequence of SEQ ID NO: 14, 16, 18, or 20; and

b) a variable heavy chain sequence of SEQ ID NO: 15, 17, 19, or 21.

11. The isolated antibody, or antigen-binding fragment thereof, of claim 9, wherein the antibody, or antigen-binding fragment thereof, binds to two or more of Frizzled 1 (Fzd1), Frizzled 2 (Fzd2), Frizzled 3 (Fzd3), Frizzled 4 (Fzd4), Frizzled 5 (Fzd5), Frizzled 6 (Fzd6), Frizzled 7 (Fzd7), Frizzled 8 (Fzd8), Frizzled 9 (Fzd9), and Frizzled 10 (Fzd10).

12. An isolated antibody, or an antigen-binding fragment thereof, that competes with the antibody of any of claims 1-11 for binding to a human Frizzled.

13. An isolated antibody, or antigen-binding fragment thereof, of any of claims 1-12, that binds to the Fzd with a KD of 50 μM or lower.

14. The isolated antibody or antigen-binding fragment of claim 13 comprising a light chain and/or heavy chain sequence of Table 6B.

15. The isolated antibody, or antigen-binding fragment thereof, of any of claims 1-14, which modulates a Wnt signaling pathway in a cell, optionally a mammalian cell.

16. The isolated antibody, or antigen-binding fragment thereof, of claim 15, which increases signaling via the Wnt signaling pathway in the cell.

17. The isolated antibody, or antigen-binding fragment thereof, of claim 15, which decreases signaling via the Wnt signaling pathway in the cell.

18. The isolated antibody, or antigen-binding fragment thereof, of any of claims 13-15, wherein the Wnt signaling pathway is a canonical Wnt signaling pathway.

19. The isolated antibody, or antigen-binding fragment thereof, of any of claims 13-16, wherein the Wnt signaling pathway is a non-canonical Wnt signaling pathway

20. An isolated polynucleotide encoding the isolated antibody, or antigen-binding fragment thereof, according to any of claims 1-19.

21. An expression vector comprising the isolated polynucleotide of claim 20.

22. An isolated host cell comprising the expression vector of claim 20.

23. A pharmaceutical composition comprising a physiologically acceptable excipient, diluent, or carrier, and a therapeutically effective amount of the isolated antibody, or antigen-binding fragment thereof, according to any of claims 1-19 or 29.

24. A method for agonizing a Wnt signaling pathway in a cell, comprising contacting the cell with the isolated antibody, or antigen-binding fragment thereof, according to claim 16.

25. The method of claim 21, wherein the antibody, or antigen-binding fragment thereof, is a fusion protein comprising a polypeptide sequence that binds LRP5 or LRP6.

26. A method for inhibiting a Wnt signaling pathway in a cell, comprising contacting the cell with the isolated antibody, or antigen-binding fragment thereof, according to claim 15.

27. A method for treating a subject having a disease or disorder associated with reduced Wnt signaling, comprising administering to the subject an effective amount

of the pharmaceutical composition of claim claim 23, wherein the isolated antibody, or antigen-binding fragment thereof is an agonist of a Wnt signaling pathway.

28. The method of claim 27, wherein the disease or disorder is selected from the group consisting of: bone fractures, stress fractures, vertebral compression fractures, osteoporosis, osteoporotic fractures, non-union fractures, delayed union fractures, spinal fusion, pre-operative optimization for spine surgeries, osteonecrosis, osseointegration of implants or orthopedic devices, osteogenesis imperfecta, bone grafts, tendon repair, tendon-bone integration, tooth growth and regeneration, maxillofacial surgery, dental implantation, periodontal diseases, maxillofacial reconstruction, osteonecrosis of the jaw, hip or femoral head, avascular necrosis, alopecia, hearing loss, vestibular hypofunction, macular degeneration, age-related macular degeneration (AMD), vitreoretinopathy, retinopathy, diabetic retinopathy, diseases of retinal degeneration, Fuchs' dystrophy, cornea diseases, stroke, traumatic brain injury, Alzheimer's disease, multiple sclerosis, diseases affecting blood brain barrier (BBB), spinal cord injuries, spinal cord diseases, oral mucositis, short bowel syndrome, inflammatory bowel diseases (IBD), Crohn's disease (CD), ulcerative colitis (UC), in particular CD with fistula formation, metabolic syndrome, dyslipidemia, diabetes, pancreatitis, exocrine pancreatic insufficiency, wound healing, diabetic foot ulcers, pressure sores, venous leg ulcers, epidermolysis bullosa, dermal hypoplasia, myocardial infarction, coronary artery disease, heart failure, hematopoietic cell disorders, immunodeficiencies, graft versus host diseases, acute kidney injuries, chronic kidney diseases, chronic obstructive pulmonary diseases (COPD), idiopathic pulmonary fibrosis, acute liver failure of all causes, acute liver failure drug-induced, alcoholic liver diseases, chronic liver failure of all causes, cirrhosis, liver fibrosis of all causes, portal hypertension, chronic liver insufficiency of all causes, end stage liver disease (ESLD), nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD) (fatty liver), alcoholic hepatitis, hepatitis C virus-induced liver diseases (HCV), hepatitis B virus-induced liver diseases (HBV), other viral hepatitis (e.g., hepatitis A virus-induced liver diseases (HAV) and hepatitis D virus-induced liver diseases (HDV)), primary biliary cirrhosis, autoimmune hepatitis, livery surgery, liver injury, liver transplantation, "small for size" syndrome in liver surgery and transplantation,

congenital liver disease and disorders, any other liver disorder or detect resulting from genetic diseases, degeneration, aging, drugs, or injuries.

29. A method for treating a subject having a disease or disorder associated with increased or enhanced Wnt signaling, comprising administering to the subject an effective amount of the pharmaceutical composition of claim 23, wherein the isolated antibody, or antigen-binding fragment thereof is an inhibitor of a Wnt signaling pathway.

30. The method of claim 27, wherein the disease or disorder is selected from the group consisting of: tumors and cancers, degenerative disorders, fibrosis of any organ or tissue, idiopathic pulmonary fibrosis, kidney fibrosis, heart failure, coronary artery disease, osteoarthritis, heterotopic ossification, osteopetrosis, congenital high bone mass disorders.

31. An isolated antibody, or an antigen-binding fragment thereof, that binds a Frizzled receptor, where the antibody or antigen-binding fragment thereof binds an epitope within a region of Frizzled 8 comprising or consisting of amino acid residues 55-137 or a corresponding region in Fzd5.

32. An isolated antibody, or an antigen-binding fragment thereof of claim 31, that binds a Frizzled receptor, wherein the antibody or antigen-binding fragment thereof contacts residues of the Frizzled receptor within a distance of:

a) less than 5 angstroms; or

b) between 5 angstroms and less than or equal to 8 angstroms.

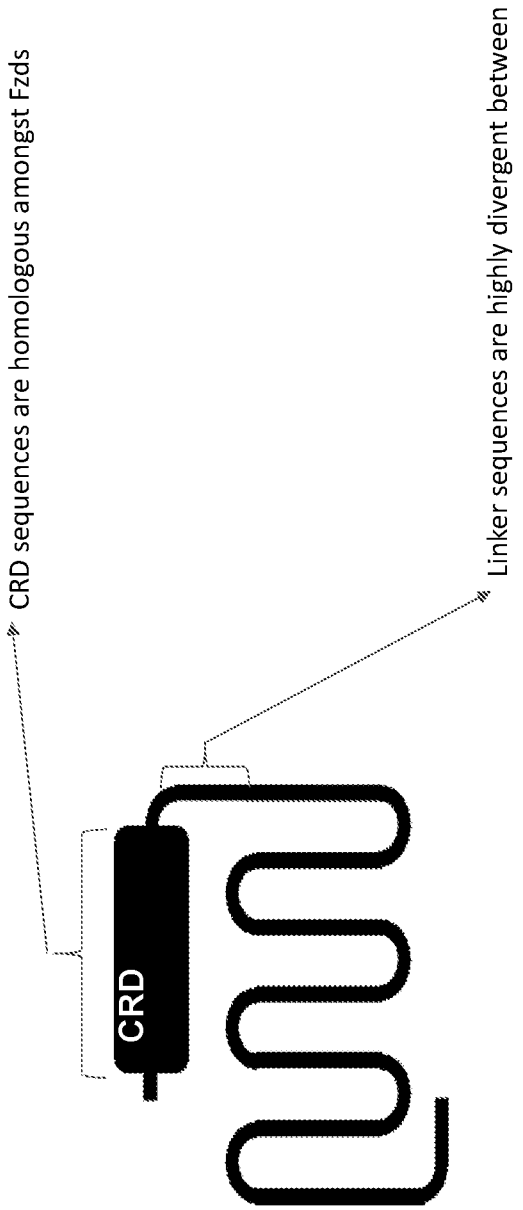

CRD sequences are homologous amongst Fzds
Linker sequences are highly divergent between different Fzd
CRD

FIG. 1

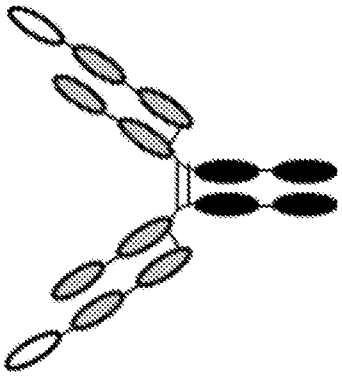


FIG. 2

```
# Percent Identity Matrix - created by Clustal2.1

    1: hFzd7-hinge   100.00   44.12   39.47
    2: hFzd1-hinge    44.12  100.00   44.68
    3: hFzd2-hinge    39.47   44.68  100.00

CLUSTAL O(1.2.4) multiple sequence alignment

hFzd7-hinge     CVGQNTSDGSGGA-----------------GGSPTAYPTAPYLPDPFTAMSPSDGRGRLS   44
hFzd1-hinge     CVGQNTSDKGTPTPSLLPEFWTSNPQHGGGGHRGGFPGGAG----------ASE-----R   45
hFzd2-hinge     CVGQNHSEDGAPALL--TTAPPPGLQPGAGGTPGG-PGGGG----------APPRYATLE   47
                ***** *: .  :                **   . * .

hFzd7-hinge     FPFSC   49
hFzd1-hinge     GKFSC   50
hFzd2-hinge     HPFHC   52
                  * *
```

FIG. 3

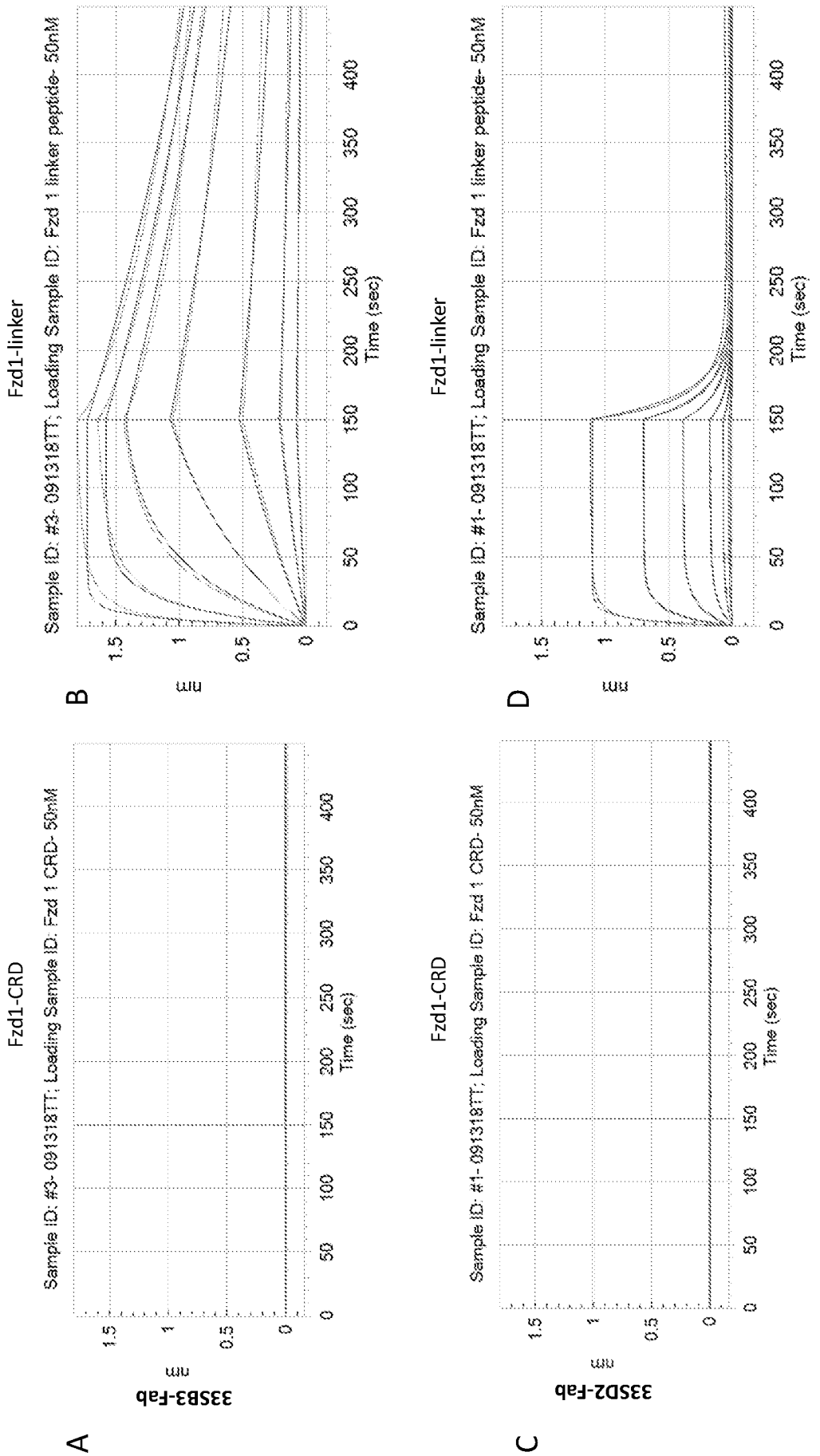

A
33SB3-Fab
nm
Fzd1-CRD
Sample ID: #3- 091318TT; Loading Sample ID: Fzd 1 CRD- 50nM
Time (sec)
B
nm
Fzd1-linker
Sample ID: #3- 091318TT; Loading Sample ID: Fzd 1 linker peptide- 50nM
Time (sec)
C
33SD2-Fab
nm
Fzd1-CRD
Sample ID: #1- 091318TT; Loading Sample ID: Fzd 1 CRD- 50nM
Time (sec)
D
nm
Fzd1-linker
Sample ID: #1- 091318TT; Loading Sample ID: Fzd 1 linker peptide- 50nM
Time (sec)

FIG. 4

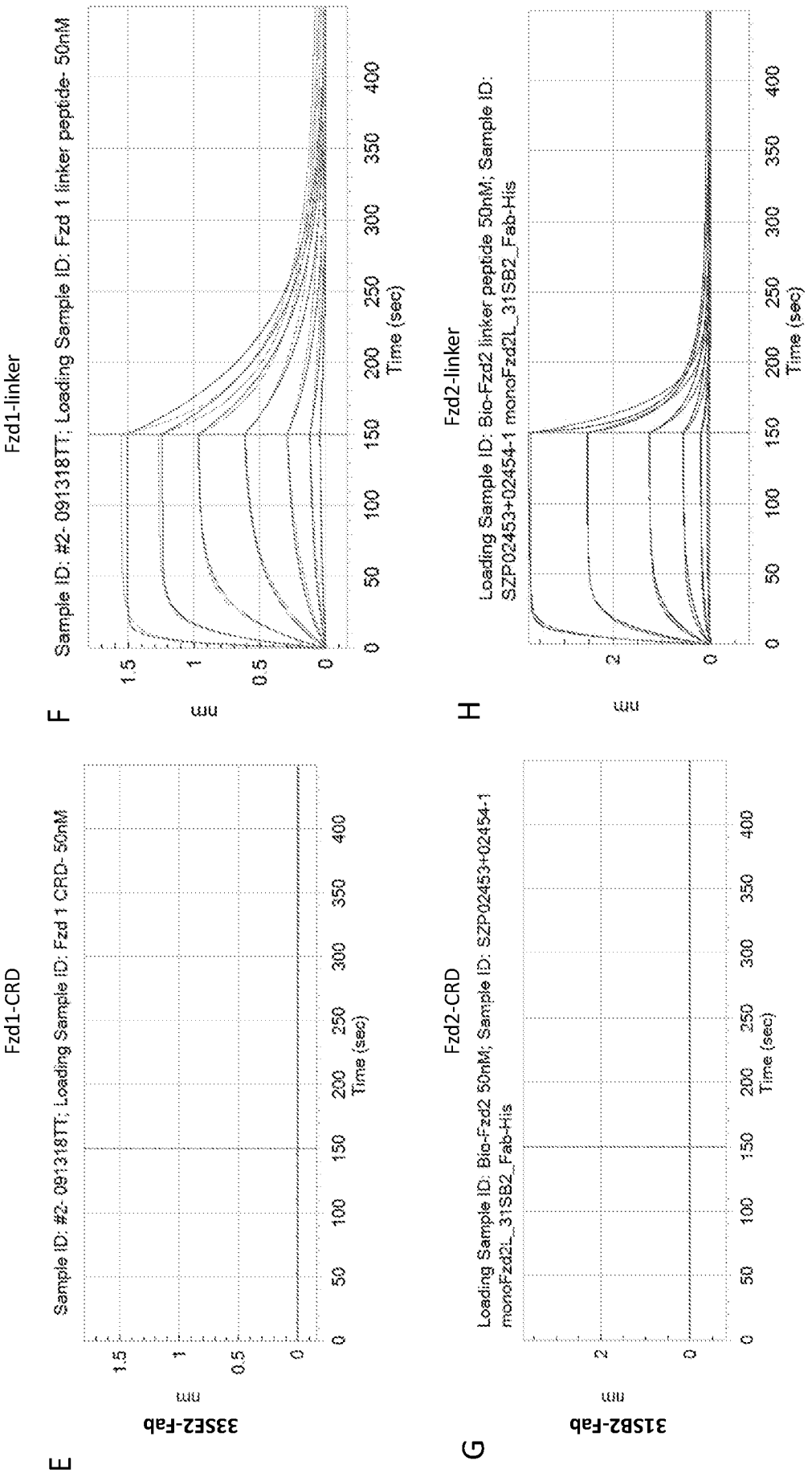
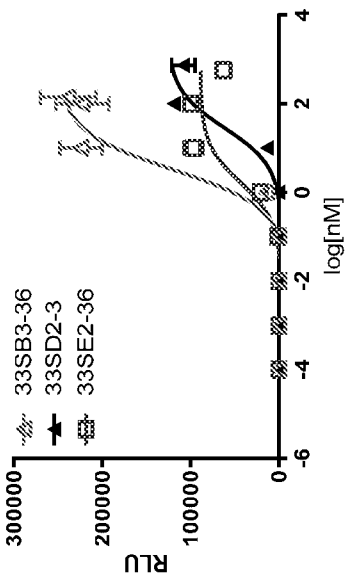

Fzd1-linker
Sample ID: #2- 091318TT; Loading Sample ID: Fzd 1 linker peptide- 50nM
nm
Time (sec)
F
Fzd2-linker
Loading Sample ID: Bio-Fzd2 linker peptide 50nM; Sample ID: SZP02453+02454-1 monoFzd2L_31SB2_Fab-His
nm
Time (sec)
H
Fzd1-CRD
Sample ID: #2- 091318TT; Loading Sample ID: Fzd 1 CRD- 50nM
nm
Time (sec)
33SE2-Fab
E
Fzd2-CRD
Loading Sample ID: Bio-Fzd2 50nM; Sample ID: SZP02453+02454-1 monoFzd2L_31SB2_Fab-His
nm
Time (sec)
31SB2-Fab
G

FIG. 4 (cont.)


A
33SB3-36
33SD2-3
33SE2-36
RLU
300000
200000
100000
0
-6
-4
-2
0
2
4
log[nM]

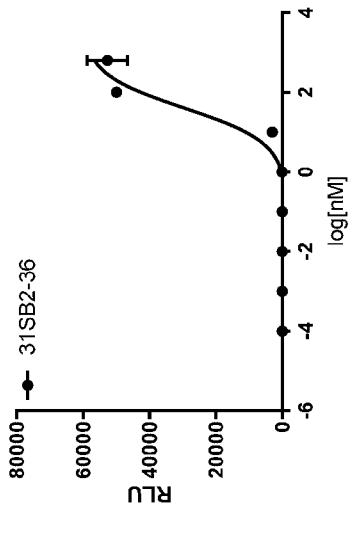
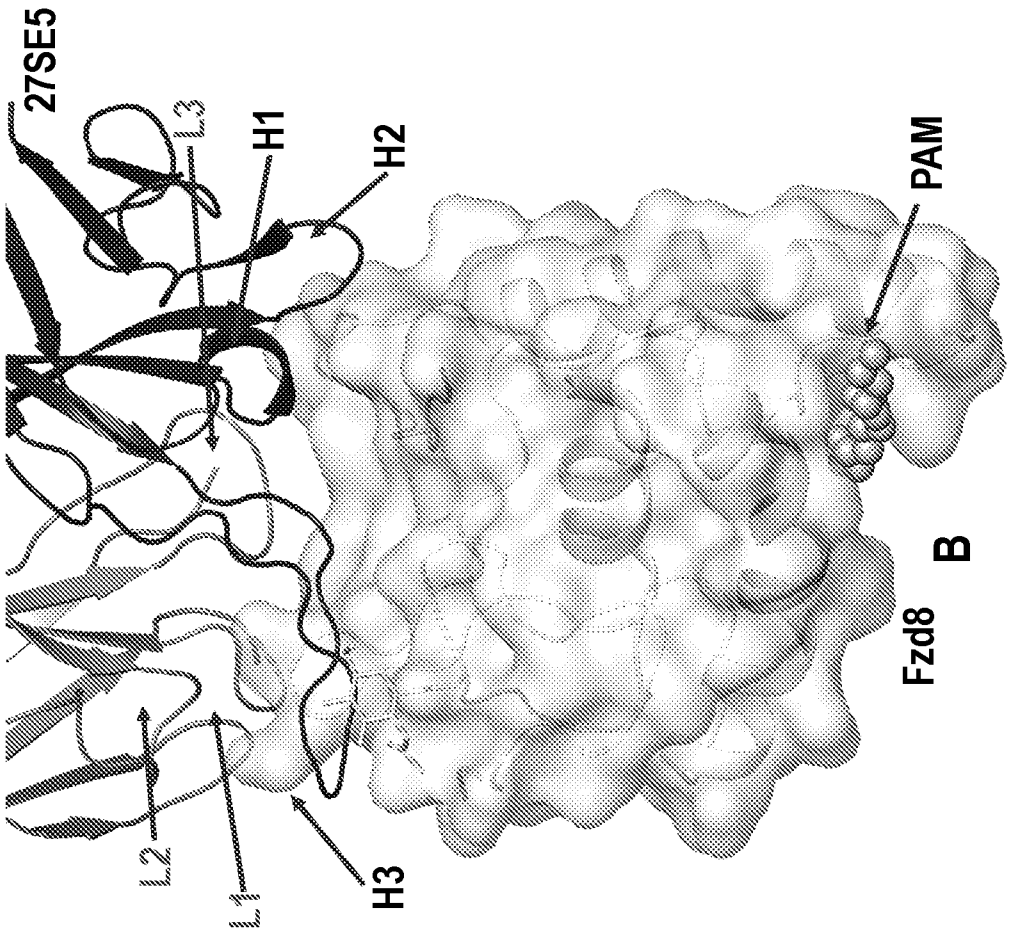

B
31SB2-36
RLU
80000
60000
40000
20000
0
-6
-4
-2
0
2
4
log[nM]

FIG. 5



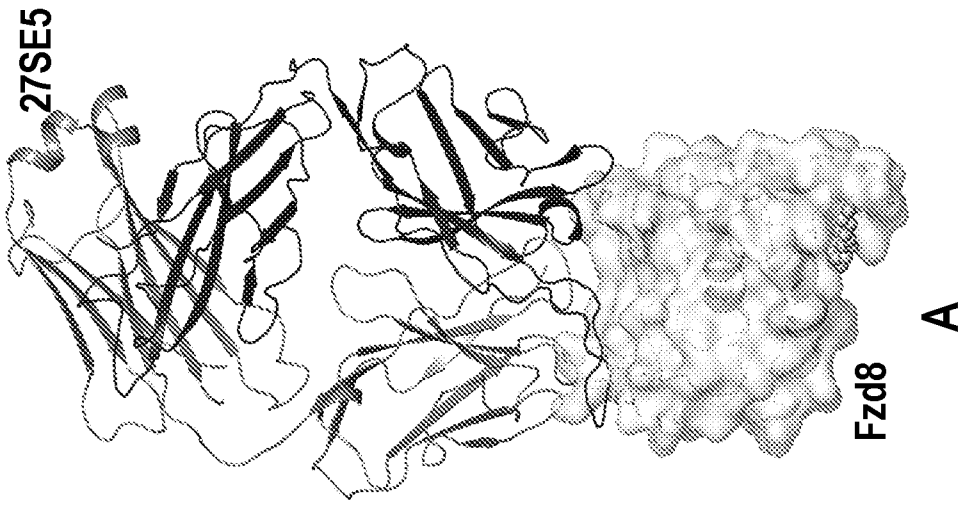


FIG .6

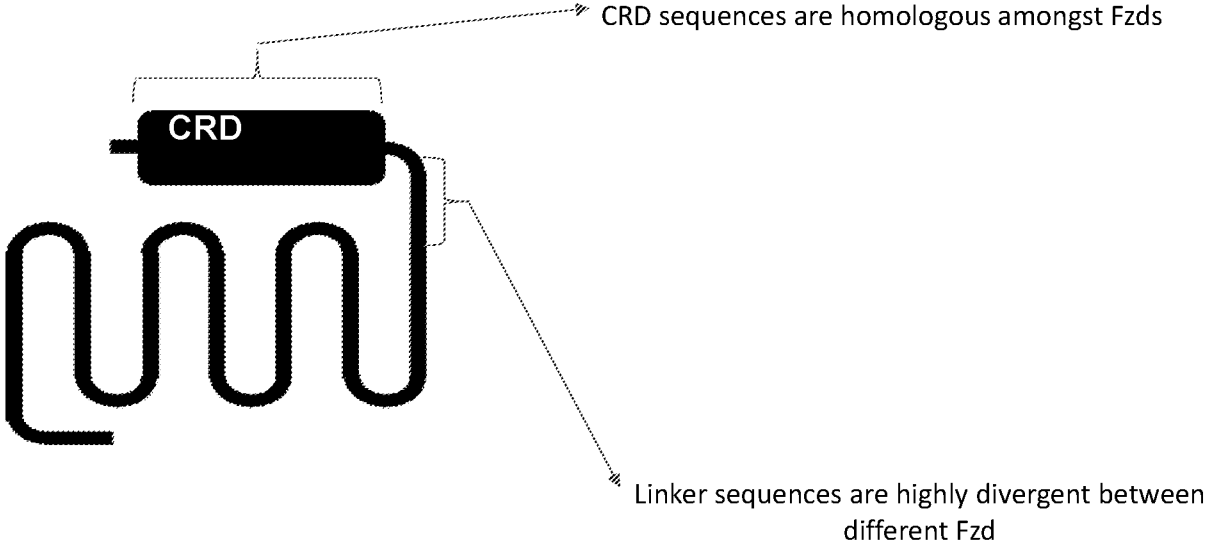

CRD sequences are homologous amongst Fzds
CRD
Linker sequences are highly divergent between different Fzd

FIG. 1